Organic Reactions

Organic Reactions

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter.   In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters.   They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work.   The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

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SUBJECTS OF PREVIOUS VOLUMES

CHAPTER 1

THE PECHMANN REACTION

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1

INTRODUCTION

H. v. Pechmann found that coumarin derivatives are formed when malic acid[1] or β-ketonic esters[2] are condensed with phenols in the presence of concentrated sulfuric acid. This reaction, which is commonly known as the Pechmann reaction, has found extensive application.

Simonis and his co-workers[3,4,5] used phosphorus pentoxide as the condensing agent in place of sulfuric acid and demonstrated that with the same reactants chromones rather than coumarins resulted. It was

shown later, however, that chromones were not always the reaction products. The condensation of a phenol and β-ketonic ester in the presence of phosphorus pentoxide is sometimes called the Simonis reaction,

[1] v. Pechmann, *Ber.*, 17, 929 (1884).
[2] Pechmann and Duisberg, *Ber.*, 16, 2119 (1883).
[3] Petschek and Simonis, *Ber.*, 46, 2014 (1913).
[4] Simonis and Lehmann, *Ber.*, 47, 692 (1914).
[5] Simonis and Remmert, *Ber.*, 47, 2229 (1914).

but it is actually merely a variation of the Pechmann reaction and will be so considered in this chapter. Other condensing agents that have been used are phosphorus oxychloride, phosphoric acid, zinc chloride, aluminum chloride, hydrogen chloride, ferric chloride, stannic chloride, titanic chloride, sodium acetate, sodium ethoxide, and boric anhydride.

By condensing appropriately substituted phenols and β-ketonic esters, coumarins can be synthesized with substituents either in the benzene nucleus or in the heterocyclic ring or in both. These compounds can then be used for the preparation of other products like coumarino-α-pyrones, coumarino-γ-pyrones, furocoumarins, chromenes, coumarones, and 2-acylresorcinols.[6] The Pechmann reaction has also been employed in the syntheses of several naturally occurring coumarins [6,7] and in the investigations of natural products like rotenone [8] and cannabinol.[9,10]

The course of this reaction depends on all of the three factors: the nature of the phenol, the nature of the β-ketonic ester, and the condensing agent.

MECHANISMS OF THE REACTIONS

Condensation of Malic Acid with Phenols. The condensation of malic acid with phenols takes place according to Pechmann [1] in three stages. The malic acid is first converted into malonaldehydic acid and formic acid, which is decomposed into water and carbon monoxide.

$$HO_2CCH(OH)CH_2CO_2H \rightarrow HCO_2H + CHOCH_2CO_2H$$
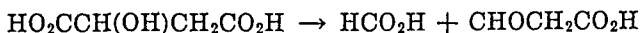
In the second stage, the union of the aldehyde with the phenol results in the formation of an unstable addition product. Two molecules of water are then eliminated, and the coumarin derivative is formed. Malonaldehydic acid contains a carbonyl group in the β position and resembles ethyl acetoacetate in its reaction with a phenol to give a coumarin.
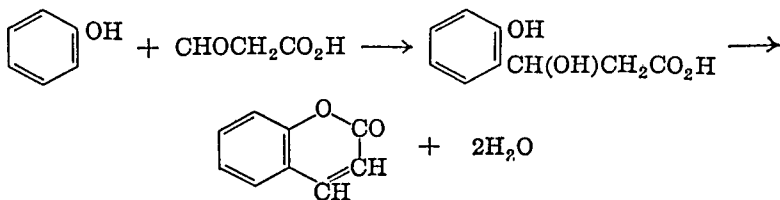
[6] Sethna and Shah, *Chem. Revs.*, **36**, 30 (1945).

[7] Späth, *Ber.*, **70A**, 83 (1937).

[8] Bridge, Crocker, Cubin, and Robertson, *J. Chem. Soc.*, **1937**, 1530.

[9] Ghosh, Todd, and Wilkinson, *J. Chem. Soc.*, **1940**, 1121.

[10] Adams and Baker, *J. Am. Chem. Soc.*, **62**, 2405 (1940).

Condensation of β-Ketonic Esters with Phenols. To explain the formation of coumarins from β-ketonic esters and phenols, Pechmann and Duisberg[2] suggested that the reactive hydrogen of the phenol in the *ortho* position to the hydroxyl group adds to the carbonyl of the β-ketonic ester to give an intermediate hydroxy ester (I). Ring closure may then take place with the elimination of a molecule of water and one of ethanol.

Ahmad and Desai[11] have pointed out that the effectiveness of such condensations depends on the reactivity of the hydrogen in the *ortho* position to the hydroxyl group and on the substituents in the β-ketonic
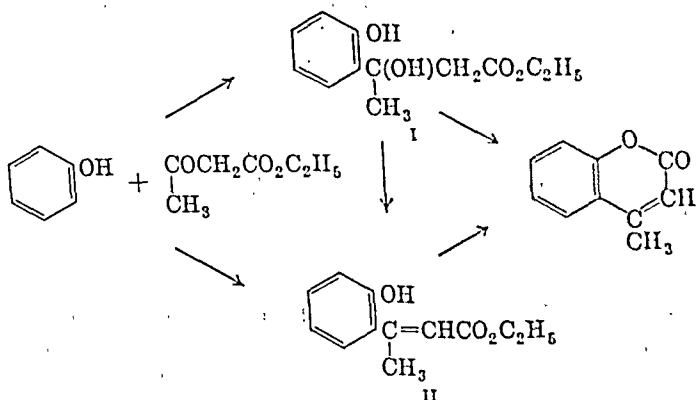
position to the hydroxyl group and on the substituents in the β-ketonic ester. The feeble tendency of phenol itself to condense is enhanced by the presence of electron-donating groups such as CH_3, OH, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, and halogens in the *meta* position to the hydroxyl group but is depressed or almost eliminated by electron-attracting groups such as NO_2, SO_3H, CO_2H, CO_2CH_3, $COCH_3$, CN, and CHO in the same position.[12] Since no intermediates have been isolated this course for the reaction is purely speculative.

A slightly different view has been advanced by Robertson and his co-workers.[13] They observed that 2-methoxy-β,4-dimethylcinnamic acid was converted into 4,7-dimethylcoumarin in the presence of 86% sulfuric acid and, further, that *m*-tolyl methyl ether and the dimethyl ether of resorcinol gave rise to 4,7-dimethylcoumarin and 7-methoxy-4-methylcoumarin, respectively. From this experimental evidence they conclude that the cinnamic acid derivative (II) is formed as an intermediate product.

[11] Ahmad and Desai, *Proc. Indian Acad. Sci.*, **6A**, 6 (1937) [*C. A.*, **32**, 559 (1938)].

[12] Desai and Ekhlas, *Proc. Indian Acad. Sci.*, **8A**, 567 (1938) [*C. A.*, **33**, 3356 (1939)].

[13] Robertson, Waters, and Jones, *J. Chem. Soc.*, **1932**, 1681.

$$H_3C\text{-}C_6H_3(OCH_3)\text{-}C(CH_3)=CHCO_2H \longrightarrow$$

(chromone structure) H_3C— benzene ring fused with O—CO ring, =CH, CH_3

$$H_3C\text{-}C_6H_4\text{-}OCH_3 \quad + \quad CH_3COCH_2CO_2C_2H_5$$
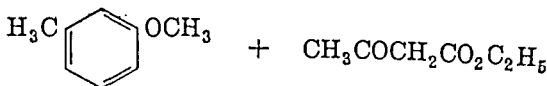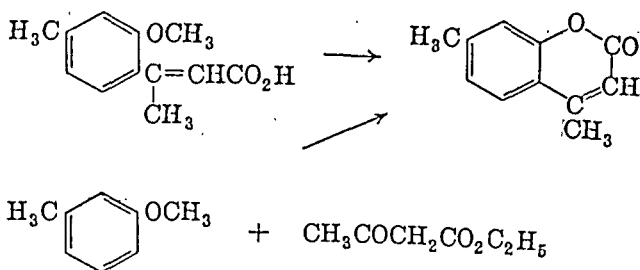
Two different mechanisms for chromone formation have been proposed. Robertson and his co-workers suggest that the first stage in the reaction results in a phenoxy acid (or its ester) by the interaction of the enolic form of the ester and phenol with the removal of a molecule of water. The phenoxy derivative then undergoes ring closure to a chromone. In support of this mechanism they cite the synthesis of

$$C_6H_5OH \; + \; \underset{C_2H_5O_2C}{\overset{HOCCH_3}{\underset{\;}{CH}}} \longrightarrow \; C_6H_5O\text{-}C(CH_2)\text{=} \cdots \quad C_2H_5O_2C$$

(chromone ring) O—CCH_3, CH, CO
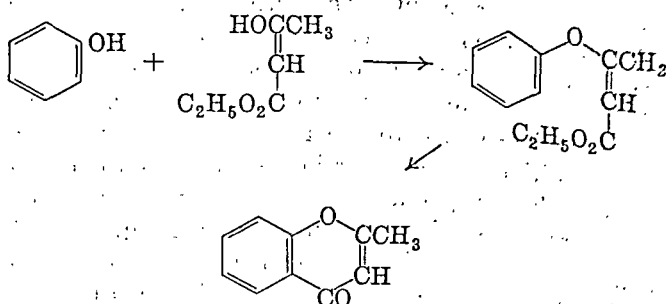
chromones from phenoxyfumaric acid and β-phenoxycinnamic acid by Ruhemann and co-workers.[14]

According to Ahmad and Desai,[11] in the formation of chromones, the reactive hydrogen of the phenolic hydroxyl reacts with the ethoxyl of the β-ketonic ester to give an aryl ester of the acid (III). This assumption is based on the evidence that only those phenols that do not contain a reactive hydrogen *ortho* to the hydroxyl group give chromones in the presence of phosphorus pentoxide as condensing agent. The aryl ester then undergoes an isomeric change analogous to the Fries migration forming an *o*-hydroxybenzoylacetone (IV) which is dehydrated to the chromone derivative (V). They assume the transformation to be possible in view of the work of Schönberg and Mustafa on Fries rearrangements with phosphorus pentoxide. They suggest also that the specific action of phosphorus pentoxide is to facilitate the formation

[14] Ruhemann and co-workers, *J. Chem. Soc.*, **77**, 984, 1119 (1900); **75**, 411, 413 (1899).
[15] Schönberg and Mustafa, *J. Chem. Soc.*, **1943**, 79.

of III or IV or both since the conversion of IV into V may be accomplished with the help of any dehydrating agent. The formation of the

III

IV V
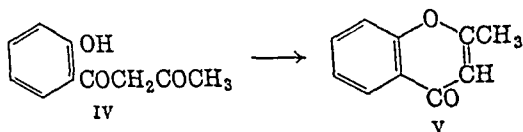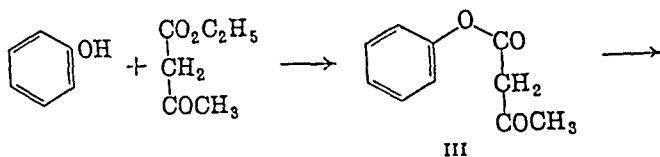
intermediate diketone IV in the syntheses of chromones by the Kostanecki acylation of o-hydroxyketones has been proved by Baker.[16]

Formation of 5-Hydroxycoumarin Derivatives in Presence of Anhydrous Aluminum Chloride. The formation of 5-hydroxycoumarin derivatives in the condensations of resacetophenone, 4-nitroresorcinol, and methyl β-resorcylate in preference to the 7-hydroxycoumarin derivatives is obviously due to the greater reactivity of the usually inaccessible 2-position of the resorcinol nucleus in these compounds. Shah and Shah [17] have explained this on the basis of chelation between the hydroxyl group and the *ortho*-substituted group, thus fixing the double bonds.[18,19,20] The point of attack is consequently the carbon atom joined by a double bond to that bearing the other hydroxyl group; resacetophenone and ethyl acetoacetate condense with the formation of 5-hydroxy-6-acetyl-4-methylcoumarin. The formation of a 5-hydroxycoumarin from methyl β-resorcylate and 4-nitroresorcinol in the presence of aluminum chloride can be explained similarly.
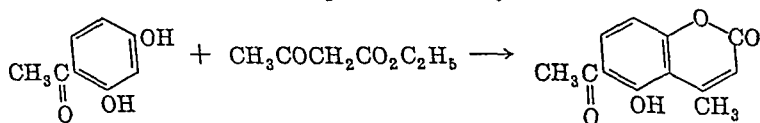
Baker [19] believes that aluminum chloride may prevent chelation; but, since 5-hydroxycoumarins are formed mainly or exclusively in good yields in the above condensations, it appears that this reagent not only fails to prevent chelation but may even promote it, for other condensing

[16] Baker, *J. Chem. Soc.*, **1933**, 1381.
[17] Shah and Shah, *J. Chem. Soc.*, **1938**, 1424.
[18] Mills and Nixon, *J. Chem. Soc.*, **1930**, 2510.
[19] Baker, *J. Chem. Soc.*, **1934**, 1684.
[20] Baker and Lothian, *J. Chem. Soc.*, **1935**, 628.

agents generally produce derivatives of 7-hydroxycoumarin. This view also finds support in the work on the formylation of methyl β-resorcylate [21] and 4-acylresorcinols; [22,23] the Gattermann reaction in the presence of anhydrous aluminum chloride in dry ether leads to formylation in the 2 position, in the case of resacetophenone yielding 2-formyl-resacetophenone.

SCOPE AND LIMITATIONS

The reactivity of the various simple and substituted phenols and β-ketonic esters in the Pechmann reaction, with sulfuric acid as the condensing agent, will be discussed first, and the role of the condensing agents second.

Reactivity of Phenols. It is found that, of the simple mono-, di-, and tri-hydric phenols, resorcinol is the most reactive, and it condenses with many substituted and cyclic β-ketonic esters. Almost equal in reactivity are phloroglucinol, α-naphthol, and pyrogallol. Phenol, quinol, and β-naphthol, however, usually give low yields of products. Phenol, for example, gives only about a 3% yield of 4-methylcoumarin on condensation with ethyl acetoacetate in the presence of sulfuric acid,[24] and it does not condense at all with many other β-ketonic esters. Catechol does not condense even with ethyl acetoacetate.

Among the substituted phenols it is found that the reactivity depends both on the nature and on the position of the substituent in the phenol. Alkyl groups in general have very little inhibiting effect in the Pechmann reaction; halogens exert somewhat more. When substituents like the nitro and the carboxyl groups are present, the reactions may not take place at all.[25,26] This is exemplified by the non-reactivity of o-, m-, or p-nitrophenol and simple phenol carboxylic acids with ethyl acetoacetate and other β-ketonic esters. The rate and degree to which a coumarin is produced depend, however, on the position of the substituent. m-Cresol condenses very readily with ethyl acetoacetate and a number of other β-ketonic esters,[27,28] p-cresol less readily,[2,28] and o-cresol not at all, even with ethyl acetoacetate.[29] m- and p-Chlorophenols react with ethyl acetoacetate, but o-chlorophenol does not react.[25] m-Dimethylamino-phenol condenses with acetonedicarboxylic acid, but the *ortho* and *para*

[21] Shah and Laiwala, *J. Chem. Soc.*, **1938**, 1828.
[22] Shah and Shah, *J. Chem. Soc.*, **1939**, 132.
[23] Shah and Shah, *J. Chem. Soc.*, **1940**, 245.
[24] Pechmann and Kraft, *Ber.*, **34**, 421 (1901).
[25] Clayton, *J. Chem. Soc.*, **93**, 2016 (1908).
[26] Dey, *J. Chem. Soc.*, **107**, 1606 (1915).
[27] Fries and Klostermann, *Ber.*, **39**, 871 (1906).
[28] Fries and Klostermann, *Ann.*, **362**, 1 (1908).
[29] Chakravarti, *J. Indian Chem. Soc.*, **9**, 31 (1932).

compounds are inert.[26] Thus in many monohydric phenols a substituent in the *ortho* position has the maximum inhibiting effect, less if the same substituent is in the *para* position, and least when it is in the *meta* position.

The influence of substituents in the resorcinol nucleus on the Pechmann reaction has been investigated. In molecules where substituents in the 4 position cause the reaction to take place with some difficulty, the same substituents in the 2 position have less effect. Resorcinols with alkyl groups in the 2 or 4 position react as readily as resorcinol. Even 4-hexadecylresorcinol condenses smoothly with ethyl acetoacetate in the presence of sulfuric acid.[30] Alkyl groups in the 5 position change the course of the reaction, and, instead of the 7-hydroxycoumarin derivatives, the 5-hydroxy isomers are obtained; an exception is in the condensation with malic acid. Thus orcinol[26, 31-35] and other 5-alkyl-resorcinols[36-38] with ethyl acetoacetate and other β-ketonic esters give 5-hydroxycoumarin derivatives. Orcinol with malic acid gives a 7-hydroxycoumarin.[39, 40, *]
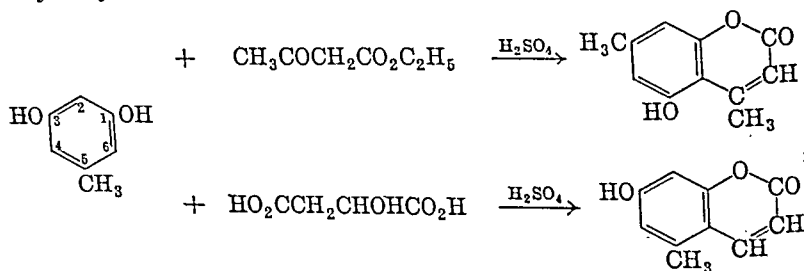
4-Chlororesorcinol condenses smoothly with a number of β-ketonic esters like ethyl α-alkylacetoacetates, ethyl benzoylacetate, and diethyl

[30] Chudgar and Shah, *J. Univ. Bombay*, **13**, Pt. 3, 18 (1944) [*C. A.*, **39**, 4078 (1945)].

[31] Krishnaswamy, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, **19A**, 5 (1944) [*C. A.*, **39**, 1153 (1945)].

[32] Pechmann and Hancke, *Ber.*, **34**, 354 (1901).

[33] Chakravarti, *J. Indian Chem. Soc.*, **8**, 407 (1931).

[34] Shah and Shah, *J. Indian Chem. Soc.*, **19**, 481 (1942).

[35] Kotwani, Sethna, and Advani, *Proc. Indian Acad. Sci.*, **15A**, 441 (1942) [*C. A.*, **37**, 624 (1943)].

[36] Russell, Todd, Wilkinson, Macdonald, and Woolfe, *J. Chem. Soc.*, **1941**, 169.

[37] Russell, Todd, Wilkinson, Macdonald, and Woolfe, *J. Chem. Soc.*, **1941**, 826.

[38] Adams, Loewe, Jelinek, and Wolff, *J. Am. Chem. Soc.*, **63**, 1971 (1941).

[39] Pechmann and Welsh, *Ber.*, **17**, 1646 (1884).

[40] Sastry, *J. Indian Chem. Soc.*, **19**, 403 (1942).

* 7-Hydroxy-4,5-dimethylcoumarin, which cannot be obtained by the direct condensation of orcinol with ethyl acetoacetate, has been prepared by the decarboxylation of 7-hydroxy-4,5-dimethylcoumarin-8-carboxylic acid formed by the condensation of *p*-orsellinic acid with ethyl acetoacetate. Sethna and Shah, *J. Indian Chem. Soc.*, **17**, 211 (1940).

The capacity of hydroquinone to undergo the Pechmann reaction is not great. When a chlorine atom is present in the hydroquinone the reaction takes place even less readily, and the presence of a bromine atom or acetyl group prevents the reaction completely. On the other hand, greater reactivity is observed when a methyl or ethyl group is substituted in the hydroquinone. 2-Methyl- and 2-ethyl-hydroquinone form coumarins with ethyl benzoylacetate and ethyl α-alkylaceto-acetates; but quinacetophenone and 2-bromohydroquinone do not condense even with ethyl acetoacetate, and 2-chlorohydroquinone reacts with difficulty. Hydroquinone, its 2-chloro- and 2-bromo-derivative, and quinacetophenone do not condense with ethyl benzoylacetate.[56]

Of the trihydroxy compounds, 4-ethylpyrogallol and ethyl pyrogallol-carboxylate condense readily with ethyl acetoacetate, ethyl α-alkyl-acetoacetates, and ethyl benzoylacetate. Gallic acid, its methyl and ethyl esters, pyrogallolcarboxylic acid, and gallacetophenone do not undergo the coumarin condensation with these same β-ketonic esters.[57]

Phloroglucinol and many of its derivatives, methylphloroglucinol,[58] dimethylphloroglucinol,[58] methyl phloroglucinolcarboxylate,[59] phloro-acetophenone, and phlorobenzophenone give coumarins with ethyl acetoacetate. The reaction with other β-ketonic esters has not been studied.

1,2,4-Triacetoxybenzene and ethyl acetoacetate in the presence of 75% sulfuric acid condense to give 6,7-dihydroxy-4-methylcoumarin.[60] No condensation of a substituted 1,2,4-trihydroxybenzene with a β-ketonic ester has been reported.

α-Naphthol derivatives with chlorine or bromine in the 4 position react with ethyl α-alkylacetoacetates and other β-ketonic esters like ethyl benzoylacetate, diethyl acetonedicarboxylate, and diethyl ace-tosuccinate. 4-Bromo-α-naphthol appears to be less reactive than 4-chloro-α-naphthol.[61] In the condensation of 4-acetyl-, 4-propionyl-, and 4-butyryl-α-naphthol with β-ketonic esters, the acyl group is elim-inated.[12] Substituted β-naphthols have not been studied.

Attempts to condense cyclohexanol and dimethyl dihydroresorcinol with acetonedicarboxylic acid did not succeed.[26]

Certain miscellaneous compounds not included in the previous dis-cussion have been condensed with malic acid and β-ketonic esters in the presence of sulfuric acid. Resorcinol and other polyhydroxyphenols

[56] Desai and Mavani, *Proc. Indian Acad. Sci.*, **15A**, 11 (1942) [*C. A.*, **36**, 6151 (1942)].
[57] Desai and Mavani, *Proc. Indian Acad. Sci.*, **15A**, 1 (1942) [*C. A.*, **36**, 6150 (1942)].
[58] Fujise and Maruyama, *J. Chem. Soc. Japan*, **55**, 1013 (1934) [*C. A.*, **29**, 4008 (1935)].
[59] Sethna, *J. Univ. Bombay*, **9** (pt. 3), 104 (1940) [*C. A.*, **35**, 6948 (1941)].
[60] Vliet, *Org. Syntheses*, **4**, 45 (1924).
[61] Chakravarti and Bagchi, *J. Indian Chem. Soc.*, **13**, 649 (1936).

will not react satisfactorily with two molecules of ethyl acetoacetate or malic acid simultaneously, but the pure hydroxycoumarins formed by the condensation of one molecule of ethyl acetoacetate or malic acid will react with a second molecule of ethyl acetoacetate or malic acid to produce coumarino-α-pyrones.[62, 63] The condensation of hydroxycoumarins with malic acid takes place more readily than with ethyl acetoacetate, though the condensation of many simpler aromatic hydroxy compounds with malic acid is more difficult than with ethyl acetoacetate. The dihydroxycoumarins derived from pyrogallol and ethyl acetoacetate will react with malic acid [63] but not with ethyl acetoacetate.

Hydroxychromones do not undergo condensation with malic acid.[64]

Hydroxythiophene derivatives react with β-ketonic esters to yield thiocoumarin derivatives.[65, 66]

$$\text{H}_3\text{C}\underset{\text{(thiophene)}}{\big[\text{S}\big]}\text{OH} + \text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 \longrightarrow \text{H}_3\text{C}\underset{\text{CH}_3}{\overset{\text{S}\quad\text{O}}{\big[\big]}}\text{CO}\text{--CH}$$
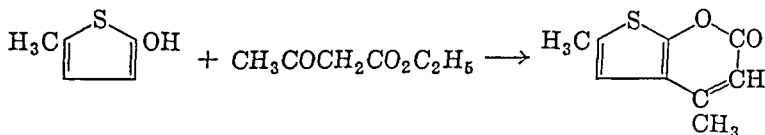
Reactivity of Malic, Maleic, and Fumaric Acids. The condensation of malic acid with phenols leads to coumarins which are unsubstituted in the pyrone ring. This procedure is therefore an alternative method for the synthesis of coumarins that are difficult to obtain by Perkin's method from o-hydroxy aromatic aldehydes. There are, however, limitations in the preparation of coumarins by this method: malic acid does not condense with many substituted phenols, and, when it does condense, the yields are often low and tarry products are obtained. Malic acid condenses only in the presence of sulfuric acid; other condensing agents fail.

Fumaric and maleic acids have been found to condense with p-cresol in the presence of sulfuric acid to give 6-methylcoumarin in good yield.[67, 68] The encouraging results in this condensation justify a more

[62] Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **6A**, 112 (1937) [*C. A.*, **32**, 559 (1938)].

[63] Sen and Chakravarti, *J. Indian Chem. Soc.*, **6**, 793 (1929).

[64] Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **9A**, 7 (1939) [*C. A.*, **33**, 4244 (1939)].

[65] Mentzer, Billet, Molho, and Dat Xuong, *Bull. soc. chim. France*, **12**, 161 (1945) [*C. A.*, **40**, 865 (1946)].

[66] Mentzer and Billet, *Bull. soc. chim. France*, **12**, 292 (1945) [*C. A.*, **40**, 2828 (1946)].

[67] Pondorff, Ger. pat. 338,737 (1921) [*C. A.*, **16**, 3488 (1922)].

[68] Thompson and Edee, *J. Am. Chem. Soc.*, **47**, 2556 (1925)

detailed investigation of the condensation of these acids with other phenols.
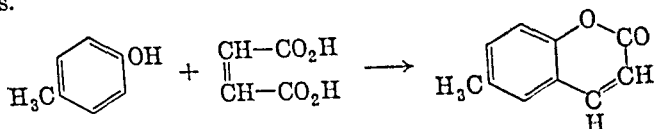
Reactivity of β-Ketonic Esters. Ethyl acetoacetate probably condenses in its enol form with the phenols. β-Ketonic esters with substituents likely to increase the enolization or stabilize the enolic form should therefore be more active than ethyl acetoacetate, and those with substituents that tend to decrease the enolization or lead to a less stable enol form should be less reactive. Substituents in a β-ketonic ester may be attached to the α-carbon atom or the γ-carbon atom, and they provide a means of obtaining coumarins with different substituents in the heterocyclic ring. Cyclic β-ketonic esters, and β-ketonic esters with heterocyclic rings, have also been condensed with phenols. The reactivities of these esters differ very widely.

Ethyl α-chloroacetoacetate has been condensed with a number of phenols to yield 3-chlorocoumarins.[26, 32, 46, 69] The condensation with this ester is smooth and the reactions closely parallel those with ethyl acetoacetate. The corresponding α-bromo ester has not been studied.

In ethyl α-alkyl- and α-aryl-acetoacetates the reactivity varies with the nature of the α substituent. With methyl, ethyl, propyl, butyl, allyl, phenyl, and benzyl groups as α substituents the condensation with reactive phenols is satisfactory, but with less reactive phenols the yields are generally poor and the condensation may be inhibited completely. Thus with m-cresol the α-ethyl derivative of ethyl acetoacetate gives a poorer yield than the α-methyl derivative; α-propyl- and α-phenyl-acetoacetates do not react.[27, 28] Ethyl α-allylacetoacetate, however, condenses with m-cresol easily.[70] β-Naphthol does not react with ethyl α-ethyl-, α-propyl-, or α-isopropyl-acetoacetate.[71] Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate with various phenols gives satisfactory results.[72, 73, 74] Thus the presence of a heavy α substituent like —CH(OH)CCl₃ does not appreciably inhibit the Pechmann reaction and has less effect than an α-ethyl substituent.

The Pechmann reaction of diethyl acetosuccinate and diethyl aceto-

[69] Chakravarti and Banerjee, *J. Indian Chem. Soc.*, **13**, 619 (1936).

[70] Naik, Desai, and Desai, *J. Indian Chem. Soc.*, **6**, 83 (1929).

[71] Chakravarti, *J. Indian Chem. Soc.*, **9**, 389 (1932).

[72] Kulkarni, Alimchandani, and Shah, *J. Indian Chem. Soc.*, **18**, 113 (1941).

[73] Kulkarni, Alimchandani, and Shah, *J. Indian Chem. Soc.*, **18**, 123 (1941).

[74] Shah and Kulkarni, *J. Univ. Bombay*, **10** (pt. 3), 86 (1941) [*C. A.*, **36**, 3796 (1942)]

glutarate, which have —$CH_2CO_2C_2H_5$ and —$CH_2CH_2CO_2C_2H_5$ as substituents in the α position, with various phenols has been systematically studied. Diethyl acetosuccinate condenses with very reactive phenols and also with m-cresol, 2-acetyl, 2-benzoyl-, and 4-chloro-resorcinol, and 4-chloro-α-naphthol, but not with phenol, o-cresol, p-cresol, hydroquinone, catechol, 4-chlorophenol, β-resorcylic acid, resacetophenone, or gallic acid.[34, 42, 75, 76] The presence of a carbethoxyalkyl group as a substituent in the β-ketonic ester results in a molecule of greater reactivity than one in which an alkyl substituent is present; diethyl acetosuccinate is as reactive as or even more reactive than the corresponding ethyl α-alkylacetoacetates. Similar observations have been made with diethyl α-acetoglutarate.[77] With substituents such as cyano or aceto the condensation takes place with the elimination of the group and the formation of the unsubstituted coumarin.[32, 46, 78]

Other α-substituted ethyl acetoacetates that have been studied are ethyl o-carboxybenzylacetoacetate,[79] ethyl phthalylacetoacetate,[79] ethyl benzoylacetoacetate,[32, 46] diethyl acetylmalonate,[32] and ethyl diacetylacetate.[32] The first two have been condensed with resorcinol and a few other reactive phenols in the presence of dry hydrogen chloride in acetic acid to form coumarin derivatives. When ethyl benzoylacetoacetate and ethyl diacetylacetate react with resorcinol, the acetyl group is removed during condensation and the same coumarins result as are formed with ethyl benzoylacetate and ethyl acetoacetate, respectively. Diethyl acetylmalonate reacts with the loss of a carbethoxyl group to give the same coumarin as that obtained by the use of ethyl acetoacetate.

A number of β-ketonic esters with groups other than methyl in the γ position have been condensed with phenols. Ethyl butyroacetate,[35] which may be considered as ethyl γ-ethylacetoacetate, and ethyl γ-phenylacetoacetate [80, 81] react with resorcinol, orcinol, pyrogallol, phloroglucinol, and α-naphthol to give 4-ethyl- and 4-benzyl-coumarin derivatives, respectively, but they do not condense with phenol, β-naphthol, hydroquinone, m-cresol, methyl β-resorcylate, or resacetophenone. A γ substituent thus reduces the reactivity.

Acetonedicarboxylic acid and its diethyl ester have been condensed with a number of simple and substituted phenols.[26, 46, 82] Citric acid gives

[75] Banerjee, J. Indian Chem. Soc., **8**, 777 (1931).
[76] Dey and Sankarnarayan, J. Indian Chem. Soc., **8**, 817 (1931).
[77] Shah and Shah, Ber., **71**, 2075 (1938).
[78] Held, Compt. rend., **116**, 720 (1893).
[79] Bülow, Ber., **38**, 474 (1905).
[80] Sonn and Litten, Ber., **66**, 1512 (1933).
[81] Kotwani, Sethna, and Advani, J. Univ. Bombay, **10** (pt. 5), 143 (1942) [C. A., **37**, 623 (1943)].
[82] Burton and Pechmann, Ann., **261**, 166 (1891).

acetonedicarboxylic acid on heating with concentrated sulfuric acid, and several workers have therefore preferred to condense citric acid with phenols instead of using pure acetonedicarboxylic acid. Phenol, nitro-phenols, phenol carboxylic acids, and *o*- and *p*-aminophenol have been found not to react. Catechol, *o*- and *p*-cresol, hydroquinone, β-naphthol, and methyl β-resorcylate gave poor yields of the corresponding coumarin, but *m*-cresol, pyrogallol, resorcinol, phloroglucinol, and α-naphthol gave good yields. Thus a molecule with the carboxyl or carbethoxy group in the γ position of ethyl acetoacetate is more reactive than one with a γ-ethyl or γ-phenyl substituent.

Ethyl γ-bromoacetoacetate and *m*-cresol, α-naphthol, or β-naphthol yield 4-bromomethylcoumarins.[83]

Among other β-ketonic esters which have been condensed with phenols are ethyl benzoylacetate,[2, 13, 32, 55, 56, 84] ethyl veratroylacetate,[85, 86] diethyl benzoylsuccinate,[87] diethyl veratroylsuccinate,[87] diethyl oxalace-tate,[26, 88, 89] diethyl oxalochloroacetate,[26, 89] diethyl oxalobromoacetate,[90] and ethyl α-formylphenylacetate. With the exception of diethyl oxal-acetate no systematic study has been made with these esters, and no generalizations are therefore possible. Unlike other β-ketonic esters, diethyl oxalacetate either does not condense or gives poor yields with certain *meta*-substituted phenols but does react more satisfactorily with certain *para*-substituted phenols; resorcinol and *m*-cresol give poor yields of coumarins, and orcinol and pyrogallol give no products. Hydroquinone, however, yields the ester of coumarin-4-carboxylic acid.

Several cyclic β-ketonic esters like ethyl cyclopentanone-2-car-boxylate[36, 48, 91] and its 4-methyl homolog,[48, 91, 92] ethyl cyclohexanone 2-carboxylate[9, 48, 93, 94, 95] and its 4-,[10, 36, 93, 96, 97] 5-,[9, 10, 38, 93, 96, 97] and 6-[93, 97] methyl homologs, ethyl 3,5-dimethyl-,[98] ethyl 4,5-dimethyl-,[98] and ethyl 5,5-dimethyl-cyclohexanone-2-carboxylate,[98] ethyl cyclohepta-none-2-carboxylate,[98] and ethyl *trans*-β-decalone-3-carboxylate[96, 97] have

[83] Dey and Sankarnarayan, *J. Indian Chem. Soc.*, **11**, 687 (1934).

[84] Robinson and Turner, *J. Chem. Soc.*, **113**, 874 (1918).

[85] Appel, Baker, Hagenbach, and Robinson, *J. Chem. Soc.*, **1937**, 738.

[86] Mitter and Paul, *J. Indian Chem. Soc.*, **8**, 271 (1931).

[87] Robinson and Rose, *J. Chem. Soc.*, **1933**, 1469.

[88] Pechmann and Graeger, *Ber.*, **34**, 378 (1901).

[89] Biginelli, *Gazz. chim. ital.*, **24**, 491 (1894).

[90] Huntress and Oleson, *J. Am. Chem. Soc.*, **70**, 2831 (1948).

[91] Ahmad and Desai, *Proc. Indian Acad. Sci.*, **5A**, 277 (1937) [*C. A.*, **31**, 5785 (1937)].

[92] Dieckmann, *Ann.*, **317**, 27 (1901).

[93] Adams, Smith, and Loewe, *J. Am. Chem. Soc.*, **63**, 1973 (1941).

[94] Sen and Basu, *J. Indian Chem. Soc.*, **5**, 467 (1928).

[95] Adams and Mecorney, *J. Am. Chem. Soc.*, **66**, 802 (1944).

[96] Chowdhry and Desai, *Proc. Indian Acad. Sci.*, **8A**, 1 (1938) [*C. A.*, **32**, 9065 (1938)].

[97] Chowdhry and Desai, *Proc. Indian Acad. Sci.*, **8A**, 12 (1938) [*C. A.*, **32**, 9066 (1938)].

[98] Adams, Loewe, Theobald, and Smith, *J. Am. Chem. Soc.*, **64**, 2653 (1942).

been condensed with phenols in the presence of sulfuric acid or phosphorus oxychloride. Chowdhry and Desai [97] report that the cyclic β-ketonic esters are more reactive than their open-chain analogs. The sluggishness of ethyl 6-methylcyclohexanone-2-carboxylate as compared with its 4-methyl and 5-methyl analogs may be attributed to the steric hindrance offered by the methyl group in the *ortho* position to the enolic hydroxyl.

Heterocyclic β-ketonic esters like ethyl chroman-3-one-4-carboxylate,[99] ethyl 8-methoxy-,[99] ethyl 3-hydroxy-6,7-dimethoxy-,[99] and ethyl 3-hydroxy-7-methoxy-Δ³-chromene-4-carboxylate,[99] ethyl β-coumaranone-2-carboxylate,[100] ethyl 5-methyl-,[100] 7-methyl-,[100] and 6-methoxy-β-coumaranone-2-carboxylate,[100] and methyl 3-hydroxyindole-2-carboxylate [100] condense with reactive phenols like resorcinol, phloroglucinol, pyrogallol, and 2-isoamylresorcinol in the presence of sulfuric acid and hydrogen chloride with formation of chromeno- and coumaronocoumarins.

Condensing Agents. The role of the condensing agent in the Pechmann reaction is very important. Condensation between a phenol and a β-ketonic ester that is not brought about in the presence of one condensing agent may be brought about by the presence of another. The yields of product with different reagents may vary markedly. Occasionally one reagent will effect the formation of one type of product and a different reagent an entirely different product.

Of the several condensing agents tested in place of sulfuric acid, only phosphorus pentoxide, phosphorus oxychloride, aluminum chloride, and to some extent zinc chloride have yielded results that require discussion.

Sulfuric Acid and Phosphorus Pentoxide. Simonis [3,4] condensed β-ketonic esters with phenols in the presence of phosphorus pentoxide and reported the formation of chromones exclusively. This conclusion was later found to be incorrect since the condensation product of resorcinol and ethyl α-methylacetoacetate, to which was assigned the structure 7-hydroxy-2,3-dimethylchromone by Simonis and Remmert,[5] was proved by Robertson and his co-workers [101] to be 7-hydroxy-3,4-dimethylcoumarin.

Jacobson and Ghosh condensed various phenols with ethyl α-phenyl- and α-benzyl-acetoacetate and with ethyl α-benzylbenzoylacetate in the presence of sulfuric acid [102,103,104] and reported the products as chromones.

[99] Hilton, O'Donell, Reed, Robertson, and Rusby, *J. Chem. Soc.*, **1936**, 423.

[100] King, Holland, Reed, and Robertson, *J. Chem. Soc.*, **1948**, 1673.

[101] Canter, Curd, and Robertson, *J. Chem. Soc.*, **1931**, 1255.

[102] Jacobson and Ghosh, *J. Chem. Soc.*, **107**, 424 (1915).

[103] Jacobson and Ghosh, *J. Chem. Soc.*, **107**, 959 (1915).

[104] Jacobson and Ghosh, *J. Chem. Soc.*, **107**, 1051 (1915).

This was due to erroneous interpretation of the results of hydrolysis of the condensation products. Baker [105,106] proved that in the reactions described by Jacobson and Ghosh only coumarins resulted.

An extensive study of the two condensing agents sulfuric acid and phosphorus pentoxide has been made, especially by Robertson [13,107,108] and Chakravarti [33,109] and their co-workers. From the results obtained so far the following generalizations can be made.

1. When sulfuric acid is used as a condensing agent a coumarin is almost always formed. However, β-naphthol and ethyl acetoacetate in the presence of sulfuric acid yield a mixture of a coumarin and a chromone in which the coumarin preponderates.[110] From 4-chloro-3,5-dimethylphenol and ethyl acetoacetate a chromone is formed exclusively.[95]

2. Phenols like resorcinol, pyrogallol, phloroglucinol, orcinol, and α-naphthol that react readily in the presence of sulfuric acid also give coumarins when phosphorus pentoxide is used as the condensing agent.

3. Phenols that do not form coumarins at all or form them in poor yields with sulfuric acid generally give chromones in the presence of phosphorus pentoxide. Thus phenol,[5] o-cresol,[4] halogenated [111] and nitro phenols,[29] halogenated and nitro cresols,[69] p-xylenol,[112] and β-naphthol,[110] which either do not condense in the presence of sulfuric acid or condense with difficulty, are found to give chromones in the presence of phosphorus pentoxide. Some phenols like catechol, for example, do not condense in the presence of either sulfuric acid or phosphorus pentoxide.

4. With phosphorus pentoxide, chromone formation is favored from β-ketonic esters with an α-alkyl substituent. If the substituent is large, the condensation may be retarded or completely inhibited. m-Cresol and p-cresol with ethyl acetoacetate in the presence of phosphorus pentoxide give the coumarins,[13,113] but with ethyl α-methyl- and α-ethyl-acetoacetate they give chromones.[3,13,113] Similar results are obtained with 4-chloro- and 4-bromo-α-naphthol.[61]

Phosphorus Oxychloride. When Naik, Desai, and Desai [70] found that α-naphthol did not condense with ethyl α-benzylacetoacetate in the presence of sulfuric acid they tried phosphorus oxychloride as condensing agent and succeeded in bringing about a reaction. Since then phosphorus oxychloride has been used frequently and in certain cases

[105] Baker, *J. Chem. Soc.*, **127**, 2349 (1925).
[106] Baker and Robinson, *J. Chem. Soc.*, **127**, 1981 (1925).
[107] Canter, Martin, and Robertson, *J. Chem. Soc.*, **1931**, 1877.
[108] Robertson, Sandrock, and Hendry, *J. Chem. Soc.*, **1931**, 2426.
[109] Chakravarti, *J. Indian Chem. Soc.*, 8, 129 (1931).
[110] Dey and Lakshminarayan, *J. Indian Chem. Soc.*, **9**, 149 (1932).
[111] Simonis and Schumann, *Ber.*, **50**, 1142 (1917).
[112] Goodall and Robertson, *J. Chem. Soc.*, **1936**, 426.
[113] Robertson and Sandrock, *J. Chem. Soc.*, **1932**, 1180.

successfully where sulfuric acid has failed.   4-Acylresorcinols and gallacetophenone do not condense with ethyl acetoacetate in the presence of sulfuric acid but condense readily in the presence of phosphorus oxychloride to give 6-acylcoumarins.[12]   Ethyl 6-methylcyclohexanone-2-carboxylate fails to react with phenols in the presence of sulfuric acid but condenses in the presence of phosphorus oxychloride to give the expected coumarin derivatives.[97]

Phosphorus oxychloride frequently gives better yields than sulfuric acid.   The condensations of resorcinol, pyrogallol, orcinol, and α-naphthol with diethyl acetosuccinate,[34] the condensations of 4-ethyl- and 4-propyl-resorcinol with ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate,[74] and the condensation of orcinol with ethyl cyclohexanone-2-carboxylate [10] may be cited as examples.

Although in general phosphorus oxychloride gives the same products as sulfuric acid, the possibility of chromone formation is not precluded. 2-Hydroxy-p-xylene gives rise to chromones on condensation with ethyl α-alkylacetoacetates and ethyl benzoylacetate in the presence of phosphorus oxychloride.[112]   4-Hydroxy-m-xylene with ethyl acetoacetate gives 4,6,8-trimethylcoumarin but with ethyl α-methyl- and α-ethyl-acetoacetate yields 2,3,6,8-tetramethyl- and 2,6,8-trimethyl-3-ethyl-chromone, respectively.[112]   These are the only instances known of chromone formation in the presence of phosphorus oxychloride. Phosphorus pentoxide gives chromones in each of these reactions.

Anhydrous Aluminum Chloride.   In exploring the use of other condensing agents for the Pechmann reaction, Sethna, Shah, and Shah [53] found that anhydrous aluminum chloride dissolved in dry ether or more generally in dry nitrobenzene not only proved to be an efficient condensing agent but also changed the course of some reactions.   If the 4 position in resorcinol is occupied by groups such as carboxyl, carbomethoxyl, acyl, or nitro, the condensation instead of giving the 7-hydroxycoumarins gives either exclusively, or mainly, 5-hydroxycoumarin derivatives.   These cannot be prepared or can be prepared only with difficulty by any other procedure.

Resacetophenone and other 4-acylresorcinols that do not condense with β-ketonic esters in the presence of sulfuric acid and that give 7-hydroxy-6-acylcoumarins in the presence of phosphorus oxychloride yield 5-hydroxy-6-acylcoumarins in the presence of anhydrous aluminum chloride.[17, 53, 114, 115]   The condensation of resacetophenone with ethyl α-methylacetoacetate, which cannot be effected by phosphorus oxychloride, takes place with ethyl α-methyl- and α-ethyl-acetoacetate in

[114] Deliwala and Shah, *J. Chem. Soc.*, 1939, 1250.
[115] Chudgar and Shah, *J. Indian Chem. Soc.*, 21, 175 (1944).

the presence of aluminum chloride.[116] 2-Acetylresorcinol and ethyl aceto-
acetate give the same coumarin and in better yield than with sulfuric
acid.[17] o-Hydroxyacetophenone, gallacetophenone, quinacetophenone,
and resacetophenone with nitro, carbomethoxyl, or aceto substituents,
however, do not react with ethyl acetoacetate in the presence of alumi-
num chloride.[17,117]
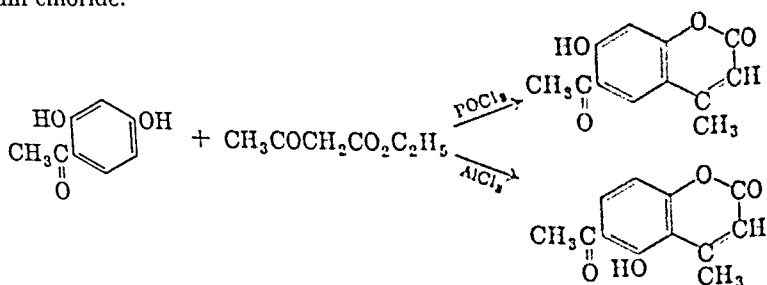
4-Nitroresorcinol with ethyl acetoacetate in the presence of sulfuric
acid yields 7-hydroxy-4-methyl-6-nitrocoumarin,[44] but in the presence
of anhydrous aluminum chloride gives 5-hydroxy-4-methyl-6-nitro-
coumarin.[118]

Methyl β-resorcylate, which condenses with ethyl acetoacetate in
the presence of sulfuric acid with formation exclusively of 7-hydroxy-
coumarin,[45] condenses in the presence of aluminum chloride to give
mainly the 5-hydroxycoumarin ester and a small quantity of the 7-
hydroxy isomer.[53]

With simple phenols the same coumarins are obtained as with sulfuric
acid. The yields are higher in some cases and lower in others. Phenol
is converted to 4-methylcoumarin in 3% yield on condensation with
ethyl acetoacetate in the presence of sulfuric acid,[24] but the same
coumarin is obtained in 40–55% yield in the presence of aluminum
chloride.[119]

In the condensation of methyl β-resorcylate with ethyl acetoacetate
in the presence of zinc chloride,[53] in the condensation of β-resorcylic
acid with malic acid in the presence of sulfuric acid,[120] and in the con-
densation of resacetophenone with ethyl acetoacetate in the presence of
phosphorus oxychloride,[12] 5-hydroxycoumarin derivatives have also
been isolated in very poor yields, the main products being the 7-hydroxy-
coumarin derivatives.

[116] Deliwala and Shah, *Proc. Indian Acad. Sci.*, 17A, 7 (1943) [*C. A.*, 37, 4379 (1943)].
[117] Deliwala and Shah, *Proc. Indian Acad. Sci.*, 13A, 352 (1941) [*C. A.*, 35, 7959 (1941)].
[118] Parekh and Shah, *J. Indian Chem. Soc.*, 19, 339 (1942).
[119] Woodruff, *Org. Syntheses*, 24, 69 (1944).
[120] Kumar, Ram, and Ray, *J. Indian Chem. Soc.*, 23, 365 (1946).

Zinc Chloride. Zinc chloride has been employed to a very limited extent as a condensing agent.[32, 121, 122] It does not appear to be superior to phosphorus oxychloride. Generally, the same coumarins are obtained as with sulfuric acid. From methyl β-resorcylate and ethyl acetoacetate in the presence of zinc chloride as the condensing agent, the 7-hydroxy-coumarin is the main product with a very small quantity of the 5-hydroxycoumarin.[53]

Hydrogen Chloride.[62, 79, 85, 99, 100, 123] The advantages of hydrogen chloride as a condensing agent lie in the avoidance of sulfonation of aromatic nuclei, prevention of saponification of the β-ketonic ester, improved yields, and purer products. However, when little or no reaction can be effected with sulfuric acid, as in the case of phenol, β-naphthol, and quinol, hydrogen chloride also gives negative results. In the condensation of ethyl α-allylacetoacetate with phenols a molecule of hydrogen chloride adds at the double bond and, instead of 3-allylcoumarins, 3,β-chloropropylcoumarins are obtained.[70, 124] A combination of zinc chloride and hydrogen chloride has been used to advantage [125, 126] in some condensations, especially in those where the other condensing agents give indifferent results. Thus ω-chlororesacetophenone, which did not condense with diethyl oxalacetate in the presence of sulfuric acid or phosphorus pentoxide, did condense in the presence of zinc chloride and dry hydrogen chloride to give β-carbethoxy-6-chloroaceto-7-hydroxycoumarin.[126]

Other Condensing Agents. Like hydrogen chloride, phosphoric acid [127] is also an effective condensing agent and does not give colored products, but it generally fails to promote condensation where sulfuric acid fails. Other condensing agents that have been reported are sodium ethoxide,[127] boric anhydride,[127] sodium acetate,[127] ferric chloride,[128] stannic chloride,[128] titanium chloride,[128] and thionyl chloride.[129] In the few condensations that have been tried with these reagents, most of them with simple phenols, the same coumarins are obtained as with sulfuric acid. The meager data available do not justify any conclusions regarding their efficacy.

[121] Pechmann and Schwarz, *Ber.*, **32**, 3699 (1899).
[122] Pechmann and Schaal, *Ber.*, **32**, 3690 (1899).
[123] Appel, *J. Chem. Soc.*, **1935**, 1031.
[124] Ahmad and Desai, *J. Univ. Bombay*, **6** (pt. 2), 89 (1937) [*C. A.*, **32**, 4561 (1938)].
[125] Borsche and Niemann, *Ber.*, **62**, 2043 (1929).
[126] Gaind, Gupta, Ray, and Sareen, *J. Indian Chem. Soc.*, **23**, 370 (1946).
[127] Chakravarti, *J. Indian Chem. Soc.*, **12**, 536 (1935).
[128] Horii, *J. Pharm. Soc. Japan*, **59**, 201 (1939) [*C. A.*, **33**, 4973 (1939)].
[129] Dixit, Kankudti, and Mulay, *J. Indian Chem. Soc.*, **22**, 207 (1945).

EXPERIMENTAL CONDITIONS AND PROCEDURES

The experimental conditions depend on the condensing agent used and are discussed under separate headings. The reaction between certain phenols, especially nitrophenols, and the β-ketonic ester may be violent.[130] Initial heating wherever necessary should therefore be gradual.

The ethyl α-alkylacetoacetates may contain ethyl acetoacetate as an impurity. They must be carefully purified, since phenols condense very readily with ethyl acetoacetate and a mixture of coumarins may result from which a pure product may be difficult to isolate. Ethyl aceto-acetate may be removed from the α-alkyl derivatives by washing with 3% sodium hydroxide solution. The washed product is then distilled.[47] This method is more satisfactory than fractional distillation under reduced pressure, especially for ethyl α-methyl- and α-ethyl-acetoacetate contaminated with ethyl acetoacetate.

Sulfuric Acid as Condensing Agent

Concentrated sulfuric acid is generally used as the condensing agent. However, 73–80% sulfuric acid is sometimes preferable as it will decrease the tendency to sulfonation. The addition of the sulfuric acid to the mixture of phenol and β-ketonic ester should be gradual, preferably with cooling, since sufficient heat may be evolved to char the product. The reaction mixture is allowed to stand overnight or for a number of days, depending on the reactivities of the phenol and the β-ketonic ester used. After the required period the reaction mixture is added slowly to cold water or crushed ice and the coumarin is precipitated. Sometimes, after the addition of sulfuric acid to the mixture of phenol and β-ketonic ester, the reaction mixture may be heated on a steam bath for some time, and then left at room temperature for one or more days. Reactions are also described in which heating on the steam bath is started immediately and continued for three to four hours, after which the reaction mixture is cooled and added to ice water. Condensations that proceed with difficulty, such as those of phenols with malic acid, are usually carried out at temperatures up to 150°. 6-Methylcoumarin was synthesized best by mixing the cresol and sulfuric acid, maintaining the mixture in a bath at 135°, and introducing the malic acid slowly.[131] The yield is generally low when heating is required, since a portion of the product may be sulfonated.

7-Hydroxycoumarin.[8] An intimate mixture of 3 g. of resorcinol, 2.46 g. of malic acid, and 6.1 ml. of concentrated sulfuric acid, after

[130] Chakravarti, J. Indian Chem. Soc., 9, 25 (1932).
[131] Bailey and Boettner, J. Ind. Eng. Chem., 13, 905 (1921).

being heated in an oil bath at 120° until the effervescence ceases (one hour), is cooled and treated with excess of crushed ice. The precipitated coumarin is purified by repeated crystallization from dilute ethanol (decolorizing carbon), from which it separates as pale pink prisms, m.p. 227–228°; yield 43%. The crude product can be conveniently decolorized by passing a stream of sulfur dioxide into a warm ethanolic solution.

The success of the method, according to Dey, Rao, and Seshadri,[132] depends primarily on the regulation of the heating. It should be stopped precisely at the moment the mixture becomes clear.

7-Hydroxy-4-methylcoumarin.[133] The preparation of this coumarin from resorcinol and ethyl acetoacetate with concentrated sulfuric acid as the condensing agent has been described in *Organic Syntheses*. The yield is 82–90%.

6,7-Dihydroxy-4-methylcoumarin.[60] The preparation of this coumarin from 1,2,4-triacetoxybenzene and ethyl acetoacetate in the presence of 75% sulfuric acid has been described in *Organic Syntheses*. The yield is 92%.

Phosphorus Pentoxide as Condensing Agent

The condensation may be carried out in the presence of this agent either in the cold if the phenol is very reactive or by heating the reaction mixture if the phenol is less reactive. The initial reaction is very vigorous, and external cooling is essential. It has been observed that the addition of a little absolute ethanol is advantageous.[33]

5-Hydroxy-4,7-dimethylcoumarin.[33] To a mixture of 5 g. of orcinol and 5 g. of ethyl acetoacetate cooled in ice, 18 g. of phosphorus pentoxide is added gradually. A vigorous reaction takes place with evolution of much heat. When the reaction ceases, the cold mass is treated with water. The precipitate is washed with water and crystallized from dilute ethanol (decolorizing carbon). It forms colorless needles, m.p. 248°.

2,5-Dimethyl-3-ethylchromone.[13] The vigorous reaction between 20 g. of *m*-cresol, 5 g. of ethyl α-ethylacetoacetate, and 20 g. of phosphorus pentoxide is controlled by agitation and occasional cooling in tap water. Then a further 10 g. of *m*-cresol and 20 g. of the pentoxide are added. The mixture is heated at 140° in an oil bath for fifteen minutes and then on the steam bath for one hour. An aqueous solution of the dark-colored product is made basic with sodium hydroxide and extracted with ether. After the evaporation of the solvent the extract is distilled under reduced pressure and the main fraction, b.p. 170–190°/20 mm., is mixed with an equal volume of light petroleum ether. 2,5-Di-

[132] Dey, Rao, and Seshadri, *J. Indian Chem. Soc.*, **11**, 746 (1934).
[133] Russell and Frye, *Org. Syntheses*, **21**, 22 (1941).

methyl-3-ethylchromone, which gradually crystallizes, is separated; and, after the removal of the solvent, the mother liquor is distilled in a vacuum. When the distillate is mixed with petroleum ether a further quantity of the solid is obtained. On recrystallization from the same solvent, the chromone forms thick, pointed prisms, m.p. 86°; yield, 1 g.

Phosphorus Oxychloride as Condensing Agent

Dry benzene or toluene is generally the solvent when phosphorus oxychloride is used as condensing agent. The reaction mixture is usually heated for a few hours on a steam bath.

7-Hydroxy-4-methyl-6-acetylcoumarin and 5-Hydroxy-4-methyl-6-acetylcoumarin.[12] A mixture of 8 g. of resacetophenone, 6 g. of ethyl acetoacetate, 2 ml. of phosphorus oxychloride, and 20 ml. of dry benzene protected from moisture is heated on a steam bath for five hours, when the evolution of hydrogen chloride ceases. After the benzene solution is poured off, the residue is extracted with two portions of 20 ml. of benzene and the solvent is removed by distillation from the combined extracts. The residue obtained from the benzene extracts is recrystallized from ethanol, and pure crystals of 7-hydroxy-4-methyl-6-acetylcoumarin, m.p. 212°, are obtained. The yield is 40%. Concentration of the ethanolic mother liquor gives a second crop of lower purity. The residue left after the removal of the solvent is repeatedly extracted with petroleum ether (b.p. 60–80°). Upon cooling, crystals deposit which on recrystallization from ethanol yield 5-hydroxy-4-methyl-6-acetylcoumarin, m.p. 164–165°.

1-Hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.[10] A solution of 6.2 g. of orcinol, 11 g. of ethyl cyclohexanone-2-carboxylate, and 4.6 ml. of phosphorus oxychloride in 45 ml. of dry benzene in an all-glass apparatus and protected from moisture is refluxed for three hours on the steam bath. The solution rapidly turns deep red, and at the end of one hour a crystalline precipitate begins to separate. Two volumes of water are added; the mixture is well shaken to destroy the phosphorus oxychloride and then cooled. Most of the product crystallizes and is obtained by filtration of the benzene-water mixture. Additional material is obtained by separation and evaporation of the benzene layer. Purification is effected by recrystallization from ethanol, m.p. 243–245°; yield, 7.6 g. (66%).

Anhydrous Aluminum Chloride as Condensing Agent

Anhydrous aluminum chloride can be used as the condensing agent either without added solvent or dissolved in dry ether or dry nitrobenzene. The best results have been reported with nitrobenzene. The

aluminum chloride is dissolved in dry, preferably freshly distilled nitrobenzene, by warming in a flask protected from moisture. This solution is added to the solution of the phenol and the β-ketonic ester in dry nitrobenzene. The reaction mixture is heated in an oil bath between 120° and 140° for an hour or two, when the evolution of hydrogen chloride almost ceases. At the end of that period the reaction mixture is cooled and the unused aluminum chloride is decomposed by the addition of ice and concentrated hydrochloric acid. The nitrobenzene is removed by steam distillation. The product remains behind. It is generally found that two moles of aluminum chloride per mole of the phenol give the best yield; more or less aluminum chloride than this quantity may decrease the yield.[53, 114] Pure anhydrous aluminum chloride dissolves in ether and nitrobenzene without leaving a residue.

Methyl 5,7-Dihydroxy-4-methylcoumarin-6-(or 8)-carboxylate.[59] Two grams of methyl phloroglucinolcarboxylate and 1.5 g. of ethyl acetoacetate are dissolved in a minimum quantity of dry ether. To this solution 3.5 g. of anhydrous aluminum chloride in 15 ml. of dry ether is added. The ether is allowed to evaporate gradually by heating the flask on a warm water bath, and the resulting homogeneous mass is heated in an oil bath between 120° and 125° for an hour until the evolution of hydrogen chloride is negligible. After cooling, dilute hydrochloric acid and ice are added. The product is purified by crystallization from ethanol. It forms clusters of tiny needles, m.p. 230–231°; yield, 1.2 g.

5-Hydroxy-4-methyl-6-propionylcoumarin.[114] A solution of 4.2 g. (1 mole) of anhydrous respropiophenone and 3.25 g. (1 mole) of ethyl acetoacetate in dry nitrobenzene is added to a solution of 6.7 g. (2 moles) of anhydrous aluminum chloride in 35 ml. of dry nitrobenzene. The mixture, protected from moisture, is heated at 120–130° until evolution of hydrogen chloride is negligible, which takes about an hour. It is then cooled, ice and 15 ml. of concentrated hydrochloric acid are added, and the nitrobenzene is steam-distilled. The brown residue is collected, decolorized by washing with a small quantity of ethanol, and crystallized from ethanol. It forms fine, silky needles, m.p. 164–165°; yield, 2 g.

Hydrogen Chloride as Condensing Agent

A solution of the phenol and the β-ketonic ester either in glacial acetic acid or in absolute ethanol [8] is saturated with hydrogen chloride while being cooled with ice water, and the reaction mixture is kept in a well-stoppered flask overnight. It is then poured into water directly or after heating for some time on a steam bath. The coumarin precipitates.

7-Hydroxy-5′-methylcoumarono-(2′,3′,3,4)-coumarin.[13] When a solution of 1 g. of ethyl 5-methyl-β-coumaranone-2-carboxylate and 1 g. of

resorcinol in methanol is saturated slowly at room temperature with hydrogen chloride a yellow solid gradually separates. After two days the mixture is heated on the steam bath for half an hour, then cooled, and the resulting coumarin is collected, washed, and crystallized from ethanol, m.p. above 300°; yield, 0.6 g.

Zinc Chloride as Condensing Agent

The condensation in the presence of zinc chloride may be carried out either with ethanol as solvent or without a solvent. Heating is essential, the period dependent on the reactivities of the phenol and the β-ketonic ester.

Ethyl 7-Dimethylaminocoumarin-4-acetate.[134] A mixture of 7 g. of distilled diethyl acetonedicarboxylate, 5 g. of m-dimethylaminophenol, 6 g. of powdered anhydrous zinc chloride, and 20 ml. of absolute ethanol is heated in a paraffin bath with refluxing for twelve hours. The resulting strongly fluorescent liquid, which deposits a small amount of a viscid solid on cooling, is poured into 400 ml. of cold water containing a little hydrochloric acid. A dark oil is precipitated, which, after it has been washed with water containing dilute hydrochloric acid and permitted to stand in contact with ethanol, solidifies slowly to a crystalline cake. The solid is crystallized first from a mixture of benzene and petroleum ether and then from absolute ethanol (decolorizing carbon). The product forms slender, colorless prisms, m.p. 133°. The yield is poor.

TABULAR SURVEY OF THE PECHMANN REACTION

All the condensations of malic acid and β-ketonic esters with phenols and miscellaneous compounds which, in the presence of various condensing agents, have resulted in the formation of either coumarins or chromones have been listed. The literature survey is complete to January, 1949.

The condensations with monohydric phenols are listed in Table I, with dihydric phenols in Table II, with trihydric phenols in Table III, with naphthols in Table IV, and with miscellaneous compounds in Table V.

The condensations with phenol itself are followed by those with monosubstituted phenols with the substituents in the following order: halogens, nitro, amino, alkyl groups in the order of increasing complexity, carboxyl and carbomethoxyl, and acyl. Then are listed the condensations with disubstituted phenols with the substituents in the same

[134] Dey. *J. Chem. Soc.*, **107**, 1643 (1915).

TABLE I

CONDENSATIONS WITH MONOHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Phenol	Malic acid	H_2SO_4 (73% & concd.)	Coumarin	Poor	1, 142
	α-Methylmalic acid	H_2SO_4 (73%)	3-Methylcoumarin	—	142
	Ethyl α-methylformylacetate	P_2O_5	3-Methylchromone	Low	143
	Ethyl acetoacetate	H_2SO_4	4-Methylcoumarin	3	2, 24
	Ethyl acetoacetate	H_2SO_4 (73%)	4-Methylcoumarin	21	144
	Ethyl sodioacetoacetate	P_2O_5	2-Methylchromone	2	5
	Ethyl acetoacetate	$AlCl_3$	4-Methylcoumarin	40-55	119
	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	3,4-Dimethylcoumarin	—	144
	Ethyl α-methylacetoacetate	P_2O_5	2,3-Dimethylchromone	25	3
	Ethyl α-ethylacetoacetate	P_2O_5	2-Methyl-3-ethylchromone	—	4
	Acetonedicarboxylic acid	H_2SO_4	Coumarin-4-acetic acid	12	138
			2-Hydroxyphenylglutaconic anhydride	—	145
	Citric acid	H_2SO_4	Coumarin-4-acetic acid	7	24
	Diethyl oxalacetate	H_2SO_4	Ethyl coumarin-4-carboxylate	—	90
	Diethyl oxalochloroacetate	H_2SO_4	Ethyl 3-chlorocoumarin-4-carboxylate	15	90
	Diethyl oxalobromoacetate	H_2SO_4	Ethyl 3-bromocoumarin-4-carboxylate	15	91
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4	Cyclopenteno-(1',2',4,3)-coumarin	5	11
	Ethyl cyclopentanone-2-carboxylate	P_2O_5	Cyclopenteno-(1',2',2,3)-chromone	—	11
o-Chloro-phenol	Ethyl α-methylacetoacetate	P_2O_5	8-Chloro-2,3-dimethylchromone	27	111
	Ethyl α-ethylacetoacetate	P_2O_5	8-Chloro-2-methyl-3-ethylchromone	—	111
	Ethyl α-propylacetoacetate	P_2O_5	8-Chloro-2-methyl-3-propylchromone	30	130
	Ethyl α-isopropylacetoacetate	P_2O_5	8-Chloro-2-methyl-3-isopropylchromone	—	130
o-Bromo-phenol	Ethyl α-methylacetoacetate	P_2O_5	8-Bromo-2,3-dimethylchromone	17	111, 130
	Ethyl α-ethylacetoacetate	P_2O_5	8-Bromo-2-methyl-3-ethylchromone	23	111
	Ethyl α-propylacetoacetate	P_2O_5	8-Bromo-2-methyl-3-propylchromone	—	130
m-Chloro-phenol	Malic acid	H_2SO_4	7-Chlorocoumarin	4	25
	Ethyl acetoacetate	H_2SO_4	7-Chloro-4-methylcoumarin	6	25
	Ethyl α-methylacetoacetate	P_2O_5	7-Chloro-2,3-dimethylchromone	23	111
	Ethyl α-ethylacetoacetate	P_2O_5	5 (or 7)-Chloro-2-methyl-3-ethyl-chromone	20	111
m-Bromo-phenol	Ethyl α-methylacetoacetate	P_2O_5	5-Bromo-2,3-dimethylchromone (7-bromo isomer also formed but not isolated)	22	111
	Ethyl α-ethylacetoacetate	P_2O_5	5 (or 7)-Bromo-2-methyl-3-ethylchromone	20	111
p-Chloro-phenol	Malic acid	H_2SO_4	6-Chlorocoumarin	3	25
	Ethyl acetoacetate	H_2SO_4	6-Chloro-4 methylcoumarin	3	25
	Ethyl α-methylacetoacetate	P_2O_5	6-Chloro-2,3-dimethylchromone	17	111, 130
	Ethyl α-ethylacetoacetate	P_2O_5	6-Chloro-2-methyl-3-ethylchromone	—	111
	Ethyl α-propylacetoacetate	P_2O_5	6-Chloro-2-methyl-3-propylchromone	—	130
	Ethyl α-isopropylacetoacetate	P_2O_5	6-Chloro-2-methyl-3-isopropylchromone	—	130
	Diethyl acetonedicarboxylate	H_2SO_4	Ethyl 6-chlorocoumarin-4-acetate	<6	26
	Diethyl oxalacetate	H_2SO_4	Ethyl 6-chlorocoumarin-4-carboxylate	—	26
	Ethyl cyclopentanone-2-carboxylate	P_2O_5	6-Chloro-2,3-dihydropentachromone	Poor	146
p-Bromo-phenol	Ethyl acetoacetate	H_2SO_4 (73%)	6-Bromo-4-methylcoumarin	—	144
	Ethyl α-methylacetoacetate	P_2O_5	6-Bromo-2,3-dimethylchromone	—	111
	Ethyl α-ethylacetoacetate	P_2O_5	6-Bromo-2-methyl-3-ethylchromone	16	111

Note: References 142-244 are listed on pp. 57-58.

TABLE I—*Continued*

CONDENSATIONS WITH MONOHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
m-Nitrophenol	Ethyl α-methylacetoacetate	P_2O_5	7-Nitro-2,3-dimethylchromone	—	29
	Ethyl α-ethylacetoacetate	P_2O_5	7-Nitro-2-methyl-3-ethylchromone	—	29
	Ethyl α-propylacetoacetate	P_2O_5	7-Nitro-2-methyl-3-propylchromone	—	29
	Ethyl α-isopropylacetoacetate	P_2O_5	7-Nitro-2-methyl-3-isopropylchromone	—	29
	Ethyl α-isobutylacetoacetate	P_2O_5	7-Nitro-2-methyl-3-isobutylchromone	—	29
p-Nitrophenol	Ethyl α-methylacetoacetate	P_2O_5	6-Nitro-2,3-dimethylchromone	—	29
	Ethyl α-ethylacetoacetate	P_2O_5	6-Nitro-2-methyl-3-ethylchromone	—	29
	Ethyl α-propylacetoacetate	P_2O_5	6-Nitro-2-methyl-3-propylchromone	—	29
	Ethyl α-isobutylacetoacetate	P_2O_5	6-Nitro-2-methyl-3-isobutylchromone	—	29
m-Aminophenol	Ethyl acetoacetate	$ZnCl_2$	7-Amino-4-methylcoumarin with varying proportions of 7(?)-hydroxylepidone, 7(?)-hydroxy-2,4,4-trimethyl-3,4-dihydroquinoline, and 4,6,6,8-tetramethyl-6,7-dihydroquinocoumarin	12–16	121
m-Methylaminophenol	Ethyl acetoacetate	$ZnCl_2$	7-Methylamino-4-methylcoumarin	65	147
m-Dimethylaminophenol	*Ethyl acetoacetate*	*$ZnCl_2$*	*7-Dimethylamino-4-methylcoumarin*	*70–75*	*122*
	Ethyl α-ethylacetoacetate	$ZnCl_2$	7-Dimethylamino-3-ethyl-4-methylcoumarin	—	122
	Diethyl acetonedicarboxylate	$ZnCl_2$	Ethyl 7-dimethylaminocoumarin-4-acetate	—	26
m-Diethylaminophenol	Ethyl acetoacetate	$ZnCl_2$	7-Diethylamino-4-methylcoumarin	—	122
o-Cresol	Ethyl acetoacetate	P_2O_5	2,8-Dimethylchromone	8	4
	Ethyl α-methylacetoacetate	P_2O_5	2,3,8-Trimethylchromone	40	4
	Ethyl α-ethylacetoacetate	P_2O_5	2,8-Dimethyl-3-ethylchromone	—	130
	Acetonedicarboxylic acid	H_2SO_4	8-Methylcoumarin-4-acetic acid	25	138
			β-2-Hydroxy-3-methylphenylglutaconic anhydride	—	
	Diethyl acetonedicarboxylate	H_2SO_4	Ethyl 8-methylcoumarin-4-acetate	—	26
m-Cresol	Malic acid	H_2SO_4	7-Methylcoumarin	27–40	27, 148
	Malic acid	H_2SO_4 (96%)	7-Methylcoumarin	54	131
	Ethyl acetoacetate	H_2SO_4	4,7-Dimethylcoumarin *	71	27
	Ethyl acetoacetate	P_2O_5	4,7-Dimethylcoumarin	8	13
	Ethyl α-chloroacetoacetate	H_2SO_4	3-Chloro-4,7-dimethylcoumarin	—	26
	Ethyl α-methylacetoacetate	H_2SO_4	3,4,7-Trimethylcoumarin	40	27
	Ethyl α-methylacetoacetate	P_2O_5	2,3,7-Trimethylchromone	10	3
	Ethyl α-methylacetoacetate	P_2O_5	2,3,5-Trimethylchromone	4	13
			2,3,7-Trimethylchromone (isolated as the styryl derivative)		
	Ethyl α-ethylacetoacetate	H_2SO_4	3-Ethyl-4,7-dimethylcoumarin	—	28
	Ethyl α-ethylacetoacetate	P_2O_5	2,5-Dimethyl-3-ethylchromone	2	13
			2,7-Dimethyl-3-ethylchromone (isolated as the styryl derivative)		
	Ethyl α-allylacetoacetate	H_2SO_4	3-Allyl-4,7-dimethylcoumarin	54	70
	Ethyl α-benzylacetoacetate	H_2SO_4	3-Benzyl-4,7-dimethylcoumarin	—	28, 105
	Diethyl acetosuccinate	H_2SO_4	Ethyl 4,7-dimethylcoumarin-3-acetate	25	34, 65
	Diethyl α-acetylglutarate	H_2SO_4 (78%)	4,7-Dimethylcoumarin-3-propionic acid	20	77

Note: References 142–244 are listed on pp. 57–58.

* If the quantity of sulfuric acid employed is less than that given in ref. 27, 4-tolyloxy-4,7-dimethylhydrocoumarin is obtained along with 4,7-dimethylcoumarin, ref. 28.

TABLE I—*Continued*

CONDENSATIONS WITH MONOHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
m-Cresol	Ethyl γ-bromoacetoacetate	H_2SO_4	7-Methyl-4-bromomethylcoumarin	—	83
(Cont'd)	Acetonedicarboxylic acid	H_2SO_4	7-Methylcoumarin-4-acetic acid	—	26
	Acetonedicarboxylic acid	H_2SO_4	7-Methylcoumarin-4-acetic acid	60	138
			β-2-Hydroxy-4-methylphenylglutaconic anhydride	—	
	Diethyl acetonedicarboxylate	H_2SO_4	7-Methylcoumarin-4-acetic acid and its ethyl and m-tolyl esters	32–43	149
	Citric acid	H_2SO_4	7-Methylcoumarin-4-acetic acid	44	150
			4,7-Dimethylcoumarin	24	
	Citric acid (hydrated)	H_2SO_4	4,7-Dimethylcoumarin	8	151
	Citric acid (dehydrated)	H_2SO_4	4,7-Dimethylcoumarin	4	151
	Citric acid	Oleum	4,7-Dimethylcoumarin	1	151
	Ethyl benzoylacetate	H_2SO_4	4-Phenyl-7-methylcoumarin	—	13
	Ethyl benzoylacetate	P_2O_5	5-Methylflavone	2	13
	Diethyl oxalacetate	H_2SO_4	Ethyl 7-methylcoumarin-4-carboxylate	Poor	26
	Diethyl chloroöxalacetate	H_2SO_4	Ethyl 3-chloro-7-methylcoumarin-4-carboxylate	—	26
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4	7-Methylcyclopenteno-(1′,2′,4,3)-coumarin	9	91
	Ethyl cyclopentanone-2-carboxylate	P_2O_5	7-Methylcyclopenteno-(1′,2′,2,3)-chromone	—	11
	Ethyl cyclohexanone-2-carboxylate	H_2SO_4	3,4-Tetrahydrobenzo-7-methylcoumarin	50	94, 152
m-Tolyl methyl ether	Ethyl acetoacetate	H_2SO_4 (86%)	4,7-Dimethylcoumarin	—	13
p-Cresol	Fumaric acid	H_2SO_4; $ZnCl_2$	6-Methylcoumarin	50	67
	Fumaric acid	H_2SO_4 (72%)	6-Methylcoumarin	40–80	68, 153
	Maleic acid	H_2SO_4; $ZnCl_2$	6-Methylcoumarin	50	67
	Malic acid	H_2SO_4	6-Methylcoumarin	32	148
	Ethyl acetoacetate	H_2SO_4	4,6-Dimethylcoumarin	40	2, 28, 154
	Ethyl acetoacetate	H_2SO_4 (80%)	4,6-Dimethylcoumarin	70	155
	Ethyl acetoacetate	P_2O_5	4,6-Dimethylcoumarin	—	113
	Ethyl acetoacetate	H_3PO_4	4,6-Dimethylcoumarin	—	127
	Ethyl α-chloroacetoacetate	H_2SO_4	3-Chloro-4,6-dimethylcoumarin	—	26
	Ethyl α-chloroacetoacetate	P_2O_5	3-Chloro-4,6-dimethylcoumarin	—	13
	Ethyl α-methylacetoacetate	H_2SO_4	3,4,6-Trimethylcoumarin	72	130
	Ethyl α-methylacetoacetate	H_2SO_4 (80%)	3,4,6-Trimethylcoumarin	—	109
	Ethyl α-methylacetoacetate	P_2O_5	2,3,6-Trimethylchromone	20	3
	Ethyl α-ethylacetoacetate	H_2SO_4 (84%)	3-Ethyl-4,6-dimethylcoumarin	7	113
	Ethyl α-ethylacetoacetate	P_2O_5	2,6-Dimethyl-3-ethylchromone	—	113, 156
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	H_2SO_4	4,6-Dimethyl-3-(α-hydroxy-β,β,β-trichloroethyl)coumarin	18	73
	Diethyl α-acetylglutarate	H_2SO_4 (78%)	4,6-Dimethylcoumarin-3-propionic acid	14	77
	Acetonedicarboxylic acid	H_2SO_4	6-Methylcoumarin-4-acetic acid	20	26
	Acetonedicarboxylic acid	H_2SO_4	6-Methylcoumarin-4-acetic acid	40	139
			β-2-Hydroxy-5-methylphenylglutaconic anhydride	—	

TABLE I—*Continued*

CONDENSATIONS WITH MONOHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
p-Cresol (*Cont'd*)	Citric acid	H_2SO_4	4,6-Dimethylcoumarin	1	151
	Ethyl benzoylacetate	H_2SO_4 (84%)	4-Phenyl-6-methylcoumarin	2	113
	Ethyl benzoylacetate	P_2O_5	6-Methylflavone	—	113
	Diethyl oxalacetate	H_2SO_4	Ethyl 6-methylcoumarin-4-carboxylate	—	26
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4	6-Methylcyclopenteno-(1',2',4,3)-coumarin	8	91
	Ethyl cyclopentanone-2-carboxylate	P_2O_5	6-Methylcyclopenteno-(1',2',2,3)-chromone	—	11
3-n-Amyl-phenol	Ethyl cyclohexanone-2-carboxylate	H_2SO_4	3-n-Amyl-7,8,9,10-tetrahydro-6-di-benzopyrone	28	157
	Ethyl 5-methylcyclohexa-none-2-carboxylate	H_2SO_4	3-n-Amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	32	157
m-Hexyl-phenol	Malic acid	H_2SO_4	7-Hexylcoumarin	39	158
2,4-Dichloro-phenol	Ethyl α-methylacetoacetate	P_2O_5	6,8-Dichloro-2,3-dimethylchromone	15	111
	Ethyl α-ethylacetoacetate	P_2O_5	6,8-Dichloro-2-methyl-3-ethylchromone	—	111, 130
2,4-Dibromo-phenol	Ethyl α-methylacetoacetate	P_2O_5	6,8-Dibromo-2,3-dimethylchromone	19	111
2-Chloro-4-methyl-phenol	Ethyl acetoacetate	H_2SO_4	8-Chloro-4,6-dimethylcoumarin	—	69
	Ethyl α-chloroacetoacetate	H_2SO_4	3,8-Dichloro-4,6-dimethylcoumarin	—	69
	Ethyl α-methylacetoacetate	H_2SO_4	8-Chloro-3,4,6-trimethylcoumarin	—	69
	Ethyl α-methylacetoacetate	P_2O_5	8-Chloro-2,3,6-trimethylchromone	—	69
	Ethyl α-ethylacetoacetate	H_2SO_4	8-Chloro-3-ethyl-4,6-dimethylcoumarin	—	69
	Ethyl α-ethylacetoacetate	P_2O_5	8-Chloro-2,6-dimethyl-3-ethylchromone	—	69
4-Chloro-2-methyl-phenol	Ethyl acetoacetate	P_2O_5	6-Chloro-2,8-dimethylchromone	—	69
	Ethyl α-methylacetoacetate	P_2O_5	6-Chloro-2,3,8-trimethylchromone	—	69
	Ethyl α-ethylacetoacetate	P_2O_5	6-Chloro-2,8-dimethyl-3-ethylchromone	—	69
	Ethyl α-propylacetoacetate	P_2O_5	6-Chloro-2,8-dimethyl-3-propylchromone	—	69
4-Chloro-3-methyl-phenol	Ethyl acetoacetate	H_2SO_4	6-Chloro-4,7-dimethylcoumarin	—	69
	Ethyl α-chloroacetoacetate	H_2SO_4	3,6-Dichloro-4,7-dimethylcoumarin	17	69, 159
	Ethyl α-methylacetoacetate	H_2SO_4	6-Chloro-3,4,7-trimethylcoumarin	—	69
	Ethyl α-methylacetoacetate	P_2O_5	6-Chloro-2,3,7-trimethylchromone	—	69
	Ethyl α-ethylacetoacetate	H_2SO_4	6-Chloro-3-ethyl-4,7-dimethylcoumarin	—	69
	Ethyl α-ethylacetoacetate	P_2O_5	6-Chloro-2,7-dimethyl-3-ethylchromone	—	69
	Ethyl α-propylacetoacetate	P_2O_5	6-Chloro-2,7-dimethyl-3-propylchromone	—	69
	Diethyl acetosuccinate	H_2SO_4	Ethyl 6-chloro-4,7-dimethylcoumarin-3-acetate	—	69
	Acetonedicarboxylic acid	H_2SO_4	6-Chloro-7-methylcoumarin-4-acetic acid	16	26, 69
	Diethyl oxalacetate	H_2SO_4	Ethyl 6-chloro-7-methylcoumarin-4-carboxylate	Excellent	26
2-Nitro-3-methyl-phenol	Ethyl acetoacetate	P_2O_5	8-Nitro-2,7-dimethylchromone	—	69
	Ethyl α-ethylacetoacetate	P_2O_5	8-Nitro-2,7-dimethyl-3-ethylchromone	—	69
4-Nitro-2-methyl-phenol	Ethyl α-methylacetoacetate	P_2O_5	6-Nitro-2,3,8-trimethylchromone	—	69
	Ethyl α-ethylacetoacetate	P_2O_5	6-Nitro-2,8-dimethyl-3-ethylchromone	—	69
	Ethyl α-propylacetoacetate	P_2O_5	6-Nitro-2,8-dimethyl-3-propylchromone	—	69
3,4-Xylenol (3,4-di-methyl-phenol)	Malic acid	H_2SO_4	6,7-Dimethylcoumarin	—	25
	Ethyl acetoacetate	H_2SO_4	4,6,7-Trimethylcoumarin	58	25
	Ethyl α-chloroacetoacetate	H_2SO_4	3-Chloro-4,6,7-trimethylcoumarin	Very good	26
	Ethyl α-methylacetoacetate	H_2SO_4	3,4,6,7-Tetramethylcoumarin	46	25
	Acetonedicarboxylic acid	H_2SO_4	6,7-Dimethylcoumarin-4-acetic acid	—	26

Note: References 142–244 are listed on pp. 57–58

ORGANIC REACTIONS

TABLE I—*Continued*

CONDENSATIONS WITH MONOHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
3,4-Xylenol (3,4-di-methyl-phenol) (*Cont'd*)	Diethyl chloroöxalacetate	H_2SO_4	Ethyl 3-chloro-6,7-dimethylcoumarin-4-carboxylate	29	26
2,3-Xylenol (2,3-di-methyl-phenol)	Ethyl α-methylacetoacetate	P_2O_5	2,3,7,8-Tetramethylchromone	—	160
2,4-Xylenol (2,4-di-methyl-phenol)	Malic acid	H_2SO_4	6,8-Dimethylcoumarin	30	25
	Ethyl acetoacetate	H_2SO_4 (concd. and 86%)	4,6,8-Trimethylcoumarin	50–97	25, 161
	Ethyl acetoacetate	P_2O_5	2,6,8-Trimethylchromone	12–18	161
	Ethyl acetoacetate	$POCl_3$	4,6,8-Trimethylcoumarin	—	112
	Ethyl α-methylacetoacetate	H_2SO_4 (concd. and 86%)	3,4,6,8-Tetramethylcoumarin	25	25, 161
	Ethyl α-methylacetoacetate	P_2O_5	2,3,6,8-Tetramethylchromone	16	161
	Ethyl α-methylacetoacetate	$POCl_3$	2,3,6,8-Tetramethylchromone	—	112
	Ethyl α-ethylacetoacetate	H_2SO_4 (86%)	4,6,8-Trimethyl-3-ethylcoumarin	—	161
	Ethyl α-ethylacetoacetate	P_2O_5	2,6,8-Trimethyl-3-ethylchromone	—	161
	Ethyl α-ethylacetoacetate	$POCl_3$	2,6,8-Trimethyl-3-ethylchromone	—	112
	Ethyl α-benzylacetoacetate	H_2SO_4 (86%)	4,6,8-Trimethyl-3-benzylcoumarin	49	161
	Ethyl benzoylacetate	H_2SO_4 (86%)	4-Phenyl-6,8-dimethylcoumarin	49	161
3,5-Xylenol (3,5-di-methyl-phenol)	Ethyl acetoacetate	H_2SO_4	4,5,7-Trimethylcoumarin	32–40	25, 95
	Ethyl α-methylacetoacetate	H_2SO_4	3,4,5,7-Tetramethylcoumarin	9–11	25, 162
	Ethyl α-methylacetoacetate	P_2O_5	2,3,5,7-Tetramethylchromone	—	163
2,5-Xylenol (2,5-di-methyl-phenol)	Malic acid	H_2SO_4	5,8-Dimethylcoumarin	—	25
	Ethyl acetoacetate	P_2O_5	2,5,8-Trimethylchromone	—	112
	Ethyl α-methylacetoacetate	P_2O_5; $POCl_3$	2,3,5,8-Tetramethylchromone	—	112, 160
	Ethyl α-ethylacetoacetate	P_2O_5; $POCl_3$	2,5,8-Trimethyl-3-ethylchromone	—	112
	Ethyl α-benzylacetoacetate	P_2O_5; $POCl_3$	2,5,8-Trimethyl-3-benzylchromone	—	112
	Ethyl benzoylacetate	P_2O_5; $POCl_3$	5,8-Dimethylflavone	—	112
Thymol	Malic acid	H_2SO_4	5-Methyl-8-isopropylcoumarin	Poor	39
Carvacrol	Ethyl acetoacetate	P_2O_5	2,8-Dimethyl-5-isopropylchromone	—	164
	Ethyl α-methylacetoacetate	P_2O_5	2,3,8-Trimethyl-5-isopropylchromone	—	164
4-Chloro-3,5-di-methyl-phenol	Ethyl acetoacetate	H_2SO_4	6-Chloro-2,5,7-trimethylchromone	35	95
2,3,5-Tri-methyl-phenol	Ethyl acetoacetate	P_2O_5	2,5,7,8-Tetramethylchromone	—	165
γ-Cumenol	Malic acid	H_2SO_4	5,6,8-Trimethylcoumarin	40	25
	Ethyl acetoacetate	H_2SO_4	4,5,6,8-Tetramethylcoumarin	12	25
	Ethyl α-methylacetoacetate	H_2SO_4	3,4,5,6,8-Pentamethylcoumarin	Poor	25

Note: References 142–244 are listed on pp. 57–58.

TABLE II

Condensations with Dihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Catechol	Acetonedicarboxylic acid	H_2SO_4	8-Hydroxycoumarin-4-acetic acid	Poor	26
Guniacol	Ethyl α-methylacetoacetate	P_2O_5	8-Methoxy-2,3-dimethylchromone	5	166
Resorcinol	Diethyl malonate	C_2H_5ONa	Ethyl 7-hydroxycoumarin-4-acetate *	—	26
	Malic acid	H_2SO_4	7-Hydroxycoumarin	43–50	1, 8, 132
	Ethyl α-phenylformylacetate	P_2O_5	7-Hydroxy-3-phenylcoumarin	—	167
	Ethyl α-phenylformylacetate	$ZnCl_2$	7-Hydroxy-3-phenylcoumarin	Poor	105
	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methylcoumarin	82–90	2, 133
	Ethyl acetoacetate	H_2SO_4 (73%)	7-Hydroxy-4-methylcoumarin	—	168
	Ethyl acetoacetate	H_2SO_4 (75%)	7-Hydroxy-4-methylcoumarin	96	169
	Ethyl acetoacetate	P_2O_5	7-Hydroxy-4-methylcoumarin	63	101
	Ethyl acetoacetate	H_3PO_4	7-Hydroxy-4-methylcoumarin	80	127
	Ethyl acetoacetate	$HCl + ZnCl_2$	7-Hydroxy-4-methylcoumarin	94	125
	Ethyl acetoacetate	HCl	7-Hydroxy-4-methylcoumarin	97	123
	Ethyl acetoacetate	$FeCl_3$	7-Hydroxy-4-methylcoumarin	57	124
	Ethyl acetoacetate	$SnCl_4$	7-Hydroxy-4-methylcoumarin	Quant.	128
	Ethyl acetoacetate	$TiCl_4$	7-Hydroxy-4-methylcoumarin	—	128
	Ethyl acetoacetate	C_2H_5ONa	7-Hydroxy-4-methylcoumarin	54	127
	Ethyl acetoacetate	CH_3CO_2Na	7-Hydroxy-4-methylcoumarin	72	127
	Ethyl acetoacetate	Boric anhydride	7-Hydroxy-4-methylcoumarin	50	127
	Ethyl acetoacetate (2 or more moles)	H_2SO_4	Dimethyldicoumarin	10	170
	Ethyl acetoacetate (2 moles)	HCl	4,4'-Dimethylcoumarino-7,8,α-pyrone	20	62
	Ethyl α-chloroacetoacetate	H_2SO_4	7-Hydroxy-3-chloro-4-methylcoumarin	—	32
	Ethyl α-chloroacetoacetate	P_2O_5	7-Hydroxy-3-chloro-4-methylcoumarin	—	109
	Methyl α-methylacetoacetate	H_2SO_4	7-Hydroxy-3,4-dimethylcoumarin	—	2
	Ethyl α-methylacetoacetate	P_2O_5	7-Hydroxy-3,4-dimethylcoumarin †	—	101, 109
	Ethyl α-methylacetoacetate	H_3PO_4; CH_3CO_2Na; C_2H_5ONa	7-Hydroxy-3,4-dimethylcoumarin	—	109, 127
	Ethyl α-ethylacetoacetate	H_2SO_4	7-Hydroxy-3-ethyl-4-methylcoumarin	—	109
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3-ethyl-4-methylcoumarin	54	101
	Ethyl α-ethylacetoacetate	P_2O_5	7-Hydroxy-3-ethyl-4-methylcoumarin	43	101, 109
	Ethyl α-propylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-propyl-4-methylcoumarin	—	109
	Ethyl α-isopropylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-isopropyl-4-methylcoumarin	—	109
	Ethyl α-butylacetoacetate	H_2SO_4 (80%)	7-Hydroxy-3-butyl-4-methylcoumarin	—	47
	Ethyl α-isobutylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-isobutyl-4-methylcoumarin	—	109
	Ethyl α-allylacetoacetate	H_2SO_4	7-Hydroxy-3-allyl-4-methylcoumarin	97	70
	Ethyl α-allylacetoacetate	HCl	7-Hydroxy-3-chloropropyl-4-methylcoumarin	87	70

Note: References 142–244 are listed on pp. 57–58.

* The formation of this product was explained by the intermediate formation of acetonetricarboxylic acid.

† Simonis and Remmert (ref. 5) carried out this condensation and assigned a chromone structure to the condensation product. Canter, Curd, and Robertson (ref. 101) have shown that the product is a coumarin derivative.

TABLE II—*Continued*

Condensations with Dihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Resorcinol (*Cont'd*)	Ethyl α-(α-hydroxy-β,β,β-tri-chloroethyl)acetoacetate	H_2SO_4 (78%)	7-Hydroxy-3-(α-hydroxy-β,β,β-tri-chloroethyl)-4-methylcoumarin	12	72
	Ethyl α-(α-hydroxy-β,β,β-tri-chloroethyl)acetoacetate	P_2O_5	7-Hydroxy-3-(α-hydroxy-β,β,β-tri-chloroethyl)-4-methylcoumarin	Poor	72
	Ethyl α-(α-hydroxy-β,β,β-tri-chloroethyl)acetoacetate	$POCl_3$	7-Hydroxy-3-(α-hydroxy-β,β,β-tri-chloroethyl)-4-methylcoumarin	36	72
	Ethyl α-phenylacetoacetate	H_2SO_4	7-Hydroxy-3-phenyl-4-methylcoumarin	—	105
	Ethyl α-phenylacetoacetate	P_2O_5	7-Hydroxy-3-phenyl-4-methylcoumarin	—	109
	Ethyl α-p-methoxyphenyl-acetoacetate	H_2SO_4	7-Hydroxy-3-p-methoxyphenyl-4-methylcoumarin	—	171
	Ethyl α-benzylacetoacetate	H_2SO_4	7-Hydroxy-3-benzyl-4-methylcoumarin	55–65	105
	Ethyl α-benzylacetoacetate	$H_2SO_4; P_2O_5;$ $H_3PO_4;$ $CH_3CO_2Na;$ C_2H_5ONa	7-Hydroxy-3-benzyl-4-methylcoumarin	—	109, 127
	Ethyl α-benzylacetoacetate	$POCl_3$	7-Hydroxy-3-benzyl-4-methylcoumarin	—	172
	Ethyl α-o-carboxybenzyl-acetoacetate	HCl	7-Hydroxy-3-o-carboxybenzyl-4-methyl coumarin	—	79
	Ethyl acetocyanoacetate	H_2SO_4	7-Hydroxy-4-methylcoumarin ‡	—	78
	Diethyl acetylmalonate	H_2SO_4	7-Hydroxy-4-methylcoumarin §	—	32, 104
	Diethyl acetosuccinate	H_2SO_4	Ethyl 7-hydroxy-4-methylcou-marin-3-acetate	30–63	75, 76
	Diethyl acetosuccinate	P_2O_5	Ethyl 7-hydroxy-4-methylcou-marin-3-acetate	Low	34, 127
	Diethyl acetosuccinate	H_3PO_4	Ethyl 7-hydroxy-4-methylcou-marin-3-acetate	—	127
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methylcou-marin-3-acetate	Quant.	34
	Diethyl acetosuccinate	$AlCl_3$	7-Hydroxy-4-methylcoumarin-3-acetic acid	Quant.	34
	Diethyl α-acetoglutarate	H_2SO_4	Ethyl 7-hydroxy-4-methylcou-marin-3-propionate	66	77
			7-Hydroxy-4-methylcoumarin-3-propionic acid	6	
	Diethyl α-acetoglutarate	P_2O_5	7-Hydroxy-4-methylcoumarin-3-propionic acid	—	173
	Diethyl α-acetoglutarate	H_3PO_4	Ethyl 7-hydroxy-4-methylcou-marin-3-propionate	—	173
			7-Hydroxy-4-methylcoumarin-3-propionic acid		
	Diethyl α-acetoglutarate	$AlCl_3$	7-Hydroxy-4-methylcoumarin-3-propionic acid	74	173
	Ethyl diacetylacetate	H_2SO_4	7-Hydroxy-4-methylcoumarin ‖	—	32
	Ethyl benzoylacetoacetate	$H_2SO_4; ZnCl_2$	7-Hydroxy-4-phenylcoumarin ‖	—	32, 104
	Ethyl benzoylacetoacetate	HCl	7-Hydroxy-4-phenylcoumarin ‖	—	174
	Ethyl phthalylacetoacetate	HCl	7-Hydroxy-4-methylcoumarin-3-benzoyl-o-carboxylic acid	—	79
	Diethyl acetonedicarboxylate	H_2SO_4	7-Hydroxycoumarin-4-acetic acid	40	82, 151

Note: References 142–244 are listed on pp. 57–58.

‡ The cyano group was eliminated.

§ A carbethoxyl group was eliminated.

‖ An acetyl group was eliminated.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Resorcinol (Cont'd)	Acetonedicarboxylic acid	P_2O_5	7-Hydroxycoumarin-4-acetic acid	23	120
			Dilactone of β,β-di(2,4-dihydroxy-phenyl)glutaric acid	42	
	Acetonedicarboxylic acid	$POCl_3$	7-Hydroxycoumarin-4-acetic acid	37	120
			Dilactone of β,β-di(2,4-dihydroxy-phenyl)glutaric acid	30	
	Acetonedicarboxylic acid	$AlCl_3$	7-Hydroxycoumarin-4-acetic acid	25	120
			Dilactone of β,β-di(2,4-dihydroxy-phenyl)glutaric acid	19	
	Acetonedicarboxylic acid	$SOCl_2$	7-Hydroxycoumarin-4-acetic acid	14	120
			Dilactone of β,β-di(2,4-dihydroxy-phenyl)glutaric acid	22	
	Ethyl α-p-methoxyphenyl-propionoacetate	H_2SO_4	7-Hydroxy-3-p-methoxyphenyl-4-ethylcoumarin	—	171
	Ethyl butyroacetate	H_2SO_4 (75%)	7-Hydroxy-4-propylcoumarin	—	35
	Ethyl α-p-methoxyphenyl-butyroacetate	H_2SO_4	7-Hydroxy-3-p-methoxyphenyl-4-propylcoumarin	—	171
	Ethyl α-p-methoxyphenyl-isovaleroacetate	H_2SO_4	7-Hydroxy-3-p-methoxyphenyl-4-isobutylcoumarin	—	171
	Ethyl α-p-methoxyphenyl-caproylacetate	H_2SO_4	7-Hydroxy-3-p-methoxyphenyl-4-amylcoumarin	—	171
	Ethyl benzoylacetate	H_2SO_4	7-Hydroxy-4-phenylcoumarin	—	2, 32
	Ethyl benzoylacetate	H_3PO_4	7-Hydroxy-4-phenylcoumarin	—	127
	Ethyl benzoylacetate	HCl	7-Hydroxy-4-phenylcoumarin	92	123
	Ethyl α-benzylbenzoylacetate	HCl	7-Hydroxy-3-benzyl-4-phenyl-coumarin	50	105
	Ethyl α-benzylbenzoylacetate	H_2SO_4	7-Hydroxy-3-benzyl-4-phenyl-coumarin	Poor	105
	Diethyl benzoylsuccinate	H_2SO_4 (85%)	Ethyl 7-hydroxy-4-phenylcou-marin-3-acetate	43	57
	Ethyl γ-phenylacetoacetate	H_2SO_4	7-Hydroxy-4-benzylcoumarin ¶	—	80, 81
	Ethyl δ-phenyl-β-ketoval-erate	H_2SO_4	7-Hydroxy-4-(phenethyl)cou-marin	—	175
	Ethyl veratroylacetate	H_2SO_4	7-Hydroxy-4-veratrylcoumarin	—	65
	Ethyl veratroylacetate	HCl	7-Hydroxy-4-veratrylcoumarin	90	65
	Ethyl trimethylgalloylacetate	H_2SO_4 (73%)	7-Hydroxy-4-(3,4,5-trimethoxy-phenyl)coumarin	—	175
	Diethyl veratroylsuccinate	H_2SO_4 (84%)	Ethyl 7-hydroxy-4-veratrylcou-marin-3-acetate	—	57
	Diethyl oxalacetate	C_2H_5ONa	Ethyl 7-hydroxycoumarin-4-car-boxylate	38-45	88
	Dimethyl oxalacetate	CH_3ONa	Methyl 7-hydroxycoumarin-4-car-boxylate	—	88
	Ethyl cyclopentanone-2-car-boxylate	H_2SO_4	7-Hydroxycyclopenteno-(1',2',4,3)-coumarin	70	91
	Ethyl 4-methylcyclopenta-none-2-carboxylate	H_2SO_4	7-Hydroxy-4'-methylcyclopenteno-(1',2',4,3)-coumarin	—	91, 92
	Ethyl cyclohexanone-2-car-boxylate	H_2SO_4	7-Hydroxy-3,4-tetrahydrobenzo-coumarin	Quant.	94, 95
	Ethyl cyclohexanone-2-car-boxylate	$POCl_3$	7-Hydroxycyclohexeno-(1',2',4',3)-coumarin	—	124

Note: References 142–244 are listed on pp. 57–58.

¶ Baker and Robinson (ref. 106) reported the preparation of this compound by the Pechmann condensation of resorcinol with the material described as ethyl γ-phenylacetoacetate by Attwood, Stevenson, and Thorpe, *J. Chem. Soc.*, **123**, 1762 (1923). This material was later found by Sonn and Litten (ref. 80) to be ethyl α-phenylacetoacetate. Therefore, their condensation product with resorcinol is 7-hydroxy-3-phenyl-4-methylcoumarin.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Resorcinol (*Cont'd*)	Ethyl 4-methylcyclohexa-none-2-carboxylate	H₂SO₄	7-Hydroxy-4'-methylcyclohexeno-(1',2',4,3)-coumarin	—	97
	Ethyl 5-methylcyclohexa-none-2-carboxylate	H₂SO₄	7-Hydroxy-5'-methylcyclohexeno-(1',2',4,3)-coumarin	—	9, 97
	Ethyl 5-methylcyclohexa-none-2-carboxylate	POCl₃	7-Hydroxy-5'-methylcyclohexeno-(1',2',4,3)-coumarin	—	97
	Ethyl 6-methylcyclohexa-none-2-carboxylate	POCl₃	7-Hydroxy-6'-methylcyclohexeno-(1',2',4,3)-coumarin	—	97
	1,2-Hydrindone-2-carboxylic acid	HCl	7-Hydroxy-4,3-indenocoumarin	10	84
	Ethyl *trans*-β-decalone-3-carboxylate	H₂SO₄	7-Hydroxy-*trans*-octalino-(2',3',4,3)-coumarin	—	97
	Ethyl indane-1,3-dione-2-car-boxylate	HCl	7-Hydroxy-1'-ketoindeno-(2',3',3,4)-coumarin	7	85
	Ethyl β-coumaranone-2-car-boxylate	H₂SO₄ (85%)	7-Hydroxycoumarono-(2',3',3,4)-coumarin	26	100
	Ethyl 5-methyl-β-coumara-none-2-carboxylate	HCl	7-Hydroxy-5'-methylcoumarono-(2',3',3,4)-coumarin	25	100
	Ethyl 7-methyl-β-coumara-none-2-carboxylate	H₂SO₄ (85%)	7-Hydroxy-7'-methylcoumarono-(2',3',3,4)-coumarin	23	100
	Ethyl 6-methoxy-β-coumara-none-2-carboxylate	HCl	7-Hydroxy-6'-methoxycoumarono-(2',3',3,4)-coumarin	—	100
	Ethyl chroman-3-one-4-car-boxylate	HCl	7-Hydroxychromeno-(3',4',4,3)-coumarin	13	99
	Ethyl 3-hydroxy-7-methoxy-3-chromene-4-carboxylate	HCl	7-Hydroxy-7'-methoxychromeno-(3',4',4,3)-coumarin	—	99
	Ethyl 3-hydroxy-8-methoxy-3-chromene-4-carboxylate	HCl; H₂SO₄ (85%)	7-Hydroxy-8'-methoxychromeno-(3',4',4,3)-coumarin	—	99
	Ethyl 3-hydroxy-6,7-dimeth-oxy-3-chromene-4-car-boxylate	H₂SO₄ (85%)	7-Hydroxy-6',7'-dimethoxychro-meno-(3',4',4,3)-coumarin	11	99
	Ethyl 3-hydroxy-6,7-dimeth-oxy-3-chromene-4-car-boxylate	HCl	7-Hydroxy-6',7'-dimethoxychro-meno-(3',4',4,3)-coumarin	9	99
	Methyl 3-hydroxyindole-2-carboxylate	H₂SO₄ (90%)	7-Hydroxyindolo-(2',3',3,4)-cou-marin	18	100
Resorcinol monomethyl ether	Malic acid	H₂SO₄	7-Methoxycoumarin	Quant.	132
	Ethyl acetoacetate	H₂SO₄; P₂O₅	7-Methoxy-4-methylcoumarin	—	130
	Acetonedicarboxylic acid	H₂SO₄	7-Methoxycoumarin-4-acetic acid	—	26
	Ethyl benzoylacetate	H₂SO₄	7-Methoxy-4-phenylcoumarin	—	84
	Ethyl veratroylacetate	H₂SO₄	7-Methoxy-4-(3',4'-dimethoxy-phenyl)coumarin	—	86
Resorcinol monobutyl ether	Ethyl cyclohexanone-2-car-boxylate	POCl₃	3-Butoxy-7,8,9,10-tetrahydro-6-dibenzopyrone	—	157
Resorcinol dimethyl ether	Ethyl acetoacetate	H₂SO₄	7-Methoxy-4-methylcoumarin **	—	130
	Ethyl acetoacetate	H₂SO₄ (80%; 87%)	7-Methoxy-4-methylcoumarin **	—	13
	Ethyl α-methylacetoacetate	H₂SO₄ (85%)	7-Methoxy-3,4-dimethylcoumarin **	—	13
4-Chloro-resorcinol	Malic acid	H₂SO₄	7-Hydroxy-6-chlorocoumarin	25	41
	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-6-chlorocou-marin	26	41
	Ethyl acetoacetate	P₂O₅	7-Hydroxy-4-methyl-6-chlorocou-marin	—	41

Note: References 142–244 are listed on pp. 57–58.

** Partial demethylation took place before the condensation.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Chloro-resorcinol (Cont'd)	Ethyl α-chloroacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3,6-dichloro-4-methyl-coumarin	—	41
	Ethyl α-methylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3,4-dimethyl-6-chloro-coumarin	—	41
	Ethyl α-ethylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-ethyl-4-methyl-6-chlorocoumarin	—	41
	Ethyl α-propylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-propyl-4-methyl-6-chlorocoumarin	—	41
	Ethyl α-isobutylacetoacetate	H_2SO_4	7-Hydroxy-3-isobutyl-4-methyl-6-chlorocoumarin	—	41
	Ethyl α-benzylacetoacetate	H_2SO_4	7-Hydroxy-3-benzyl-4-methyl-6-chlorocoumarin	—	41
	Diethyl acetosuccinate	H_2SO_4	Ethyl 7-hydroxy-4-methyl-6-chloro-coumarin-3-acetate	—	41, 42
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methyl-6-chloro-coumarin-3-acetate	—	42
	Acetonedicarboxylic acid	H_2SO_4	7-Hydroxy-6-chlorocoumarin-4-acetic acid	—	41
	Ethyl benzoylacetate	H_2SO_4	7-Hydroxy-4-phenyl-6-chlorocoumarin	—	41
4-Bromo-resorcinol	Ethyl acetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-4-methyl-6-bromocoumarin	—	43, 177
	Ethyl α-methylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3,4-dimethyl-6-bromo-coumarin	—	43
	Ethyl α-ethylacetoacetate	H_2SO_4; P_2O_5	7-Hydroxy-3-ethyl-4-methyl-6-bromocoumarin	—	43
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methylcoumarin-3-acetate	—	42
2-Nitro-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-8-nitrocoumarin	60	41
	Ethyl α-methylacetoacetate	H_2SO_4	7-Hydroxy-3,4-dimethyl-8-nitro-coumarin	15	41
4-Nitro-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-6-nitrocoumarin	—	44
	Ethyl acetoacetate	$AlCl_3$	5-Hydroxy-4-methyl-6-nitrocoumarin	3	118
2-Amino-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-8-aminocoumarin	—	177
2-Methyl-resorcinol	Malic acid	H_2SO_4	7-Hydroxy-8-methylcoumarin	—	178
	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4,8-dimethylcoumarin	—	62
	Ethyl benzoylacetate	H_2SO_4	7-Hydroxy-4-phenyl-8-methylcoumarin	89	179
4-Methyl-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4,6-dimethylcoumarin	Quant.	180
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4,6-dimethylcou-marin-3-acetate	—	181
5-Methyl-resorcinol (orcinol)	Malic acid	H_2SO_4	7-Hydroxy-5-methylcoumarin	Good	39, 40
	Ethyl acetoacetate	H_2SO_4	5-Hydroxy-4,7-dimethylcoumarin ††	91	31
	Ethyl acetoacetate	H_2SO_4 (73%)	5-Hydroxy-4,7-dimethylcoumarin ††	68	168
	Ethyl acetoacetate	P_2O_5	5-Hydroxy-4,7-dimethylcoumarin	—	33
	Ethyl acetoacetate	H_3PO_4 (concd. and 85%)	5-Hydroxy-4,7-dimethylcoumarin	55	127, 182

Note: References 142–244 are listed on pp. 57–58.

†† Müller (ref. 151) who also carried out these condensations, assigned the 7-hydroxycoumarin structure to the product. This is incorrect as the product was shown earlier, by Collie and Chrystall, *J. Chem. Soc.*, **91**, 1804 (1907), to have the 5-hydroxycoumarin structure.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
5-Methyl-resorcinol (orcinol) (Cont'd)	Ethyl α-chloroacetoacetate	H_2SO_4	5-Hydroxy-3-chloro-4,7-dimethyl-coumarin	60	32
	Ethyl α-chloroacetoacetate	P_2O_5	5-Hydroxy-3-chloro-4,7-dimethyl-coumarin	—	33
	Ethyl α-methylacetoacetate	P_2O_5	5-Hydroxy-3,4,7-trimethylcoumarin	—	33
	Ethyl α-ethylacetoacetate	H_2SO_4	5-Hydroxy-3-ethyl-4,7-dimethyl-coumarin	—	33
	Ethyl α-butylacetoacetate	H_2SO_4	5-Hydroxy-3-butyl-4,7-dimethyl-coumarin	—	37
	Ethyl α-butylacetoacetate	$POCl_3$	5-Hydroxy-3-butyl-4,7-dimethyl-coumarin	62	182
	Ethyl α-allylacetoacetate	HCl	5-Hydroxy-3-(β-chloropropyl)-4,7-dimethylcoumarin	—	124
	Ethyl α-(α-hydroxy-β,β,β-tri-chloroethyl)acetoacetate	$POCl_3$	5-Hydroxy-3-(α-hydroxy-β,β,β-tri-chloroethyl)-4,7-dimethylcou-marin	30	72
	Ethyl α-benzylacetoacetate	H_2SO_4	7-Hydroxy-3-benzyl-4,5-dimethyl-coumarin ‡‡	—	105
	Diethyl acetosuccinate	H_2SO_4; P_2O_5; H_3PO_4	Ethyl 5-hydroxy-4,7-dimethylcou-marin-3-acetate	—	34, 127
	Diethyl acetosuccinate	$POCl_3$	Ethyl 5-hydroxy-4,7-dimethylcou-marin-3-acetate	67	34
	Diethyl α-acetoglutarate	H_2SO_4	Ethyl 5-hydroxy-4,7-dimethylcou-marin-3-propionate and 5-hy-droxy-4,7-dimethylcoumarin-3-propionic acid	—	77
	Diethyl α-acetoglutarate	P_2O_5	5-Hydroxy-4,7-dimethylcoumarin-3-propionic acid	—	173
	Diethyl α-acetoglutarate	HCl	Ethyl 5-hydroxy-4,7-dimethylcou-marin-3-propionate and 5-hy-droxy-4,7-dimethylcoumarin-3-propionic acid	—	77, 173
	Acetonedicarboxylic acid	H_2SO_4	5-Hydroxy-7-methylcoumarin-4-acetic acid	Good	26
	Citric acid	H_2SO_4	5-Hydroxy-7-methylcoumarin-4-acetic acid and orcin-aurin	—	151
	Ethyl butyroacetate	H_2SO_4 (75%)	5-Hydroxy-4-propyl-7-methylcou-marin	—	35
	Ethyl γ-phenylacetoacetate	H_2SO_4 (80%)	5-Hydroxy-4-benzyl-7-methylcou-marin	—	81
	Ethyl α-benzylbenzoylacetate	$ZnCl_2$	5-Hydroxy-3-benzyl-4-phenyl-7-methylcoumarin §§	—	103
	Ethyl cyclopentanone-2-car-boxylate	H_2SO_4	5-Hydroxy-7-methyl-3,4-cyclo-pentenocoumarin	—	36
	Ethyl cyclopentanone-2-car-boxylate	$POCl_3$	5-Hydroxy-7-methylcyclopenteno-(1',2',4,3)-coumarin	57	91
	Ethyl 4-methylcyclopenta-none-2-carboxylate	$POCl_3$	5-Hydroxy-7,4'-dimethylcyclo-penteno-(1',2',4,3)-coumarin	—	91
	Ethyl cyclohexanone-2-car-boxylate	H_2SO_4	1-Hydroxy-3-methyl-7,8,9,10-tetra-hydro-6-dibenzopyrone	35	10

Note: References 142–244 are listed on pp. 57–58.

‡‡ By analogy with the other compounds obtained in the condensation of orcinol with β-ketonic esters, this compound is probably a 5-hydroxycoumarin derivative.

§§ By analogy with the other compounds obtained in the condensation of orcinol with β-ketonic esters, this compound is probably a 5-hydroxycoumarin derivative. The structure originally assigned (7-hydroxy-3-benzyl-4-phenyl-5-methyl-coumarin) is incorrect; refs. 105, 106.

TABLE II—*Continued*

Condensations with Dihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
5-Methyl-resorcinol (orcinol) (*Cont'd*)	Ethyl cyclohexanone-2-carboxylate	POCl₃	5-Hydroxy-7-methylcyclohexeno-(1′,2′,4,3)-coumarin	—	124
	Ethyl cyclohexanone-2-carboxylate	POCl₃	1-Hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	66	10
	Ethyl 4-methylcyclohexanone-2-carboxylate	POCl₃	5-Hydroxy-7,4′-dimethylcyclohexeno-(1′,2′,4,3)-coumarin	—	97
	Ethyl 5-methylcyclohexanone-2-carboxylate	H₂SO₄; POCl₃	5-Hydroxy-7,5′-dimethylcyclohexeno-(1′,2′,4,3)-coumarin ‖‖	—	97
	Ethyl 5-methylcyclohexanone-2-carboxylate	POCl₃	1-Hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone	62	10
	Ethyl 6-methylcyclohexanone-2-carboxylate	POCl₃	5-Hydroxy-7,6′-dimethylcyclohexeno-(1′,2′,4,3)-coumarin	—	97
	Ethyl *trans-β*-decalone-3-carboxylate	H₂SO₄	5-Hydroxy-7-methyl-*trans*-octalino-(2′,3′,4,3)-coumarin	—	97
2-Ethyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-ethylcoumarin	79	183
4-Ethyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-6-ethylcoumarin	49–Quant.	184, 185
	Ethyl acetoacetate	H₂SO₄ (73%)	7-Hydroxy-4-methyl-6-ethylcoumarin	80–85	186
	Ethyl α-methylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3,4-dimethyl-6-ethylcoumarin	90	55
	Ethyl α-methylacetoacetate	POCl₃	7-Hydroxy-3,4-dimethyl-6-ethylcoumarin	—	187
	Ethyl α-ethylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3,6-diethyl-4-methylcoumarin	75	55
	Ethyl α-ethylacetoacetate	POCl₃	7-Hydroxy-3,6-diethyl-4-methylcoumarin	—	187
	Ethyl α-propylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3-propyl-4-methyl-6-ethylcoumarin	65	55
	Ethyl α-propylacetoacetate	POCl₃	7-Hydroxy-3-propyl-4-methyl-6-ethylcoumarin	—	187
	Ethyl α-butylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3-butyl-4-methyl-6-ethylcoumarin	—	55
	Ethyl α-butylacetoacetate	POCl₃	7-Hydroxy-3-butyl-4-methyl-6-ethylcoumarin	—	187
	Ethyl α-allylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3-allyl-4-methyl-6-ethylcoumarin	45	55
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	H₂SO₄ (80%)	7-Hydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methyl-6-ethyl-coumarin	Poor	74
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	POCl₃	7-Hydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methyl-6-ethylcoumarin	27	74
	Diethyl acetosuccinate	H₂SO₄ (80%)	Ethyl 7-hydroxy-4-methyl-6-ethyl-coumarin-3-acetate	38	181
	Diethyl acetosuccinate	POCl₃	Ethyl 7-hydroxy-4-methyl-6-ethyl-coumarin-3-acetate	76	181
	Ethyl benzoylacetate	H₂SO₄ (73%)	7-Hydroxy-4-phenyl-6-ethylcoumarin	90	55
	Ethyl cyclopentanone-2-carboxylate	H₂SO₄	7-Hydroxy-6-ethylcyclopenteno-(1′,2′,4,3)-coumarin	32	91

Note: References 142–244 are listed on pp. 57–58.

‖‖ Sen and Basu (ref. 94) have carried out the same condensation and assigned the 7-hydroxy structure to the condensation product. Chowdhry and Desai (ref. 97) have shown this to be incorrect and have assigned the 5-hydroxy-coumarin structure.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Ethyl-resorcinol (*Cont'd*)	Ethyl 4-methylcyclopentanone-2-carboxylate	H_2SO_4	7-Hydroxy-4'-methyl-6-ethylcyclopenteno-(1',2',4,3)-coumarin	—	91
	Ethyl cyclohexanone-2-carboxylate	$POCl_3$	7-Hydroxy-6-ethylcyclohexeno-(1',2',4,3)-coumarin	—	124
	Ethyl 4-methylcyclohexanone-2-carboxylate	H_2SO_4	7-Hydroxy-4'-methyl-6-ethylcyclohexeno-(1',2',4,3)-coumarin	—	96
	Ethyl 5-methylcyclohexanone-2-carboxylate	H_2SO_4	7-Hydroxy-5'-methyl-6-ethylcyclohexeno-(1',2',4,3)-coumarin	—	96
	Ethyl 6-methylcyclohexanone-2-carboxylate	$POCl_3$	7-Hydroxy-6'-methyl-6-ethylcyclohexeno-(1',2',4,3)-coumarin	—	97
	Ethyl *trans*-β-decalone-3-carboxylate	H_2SO_4	7-Hydroxy-6-ethyl-*trans*-octalino-(2',3',4,3)-coumarin	—	96
5-Ethyl-resorcinol	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	5-Hydroxy-5'-methyl-7-ethyl-3,4-cyclohexenocoumarin	—	37
4-Propyl-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-6-propyl-coumarin	—	185
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	$POCl_3$	7-Hydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methyl-6-propyl-coumarin	Low	74
	Diethyl acetosuccinate	H_2SO_4	Ethyl 7-hydroxy-4-methyl-6-propyl-coumarin-3-acetate	38	181
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methyl-6-propyl-coumarin-3-acetate	Quant.	181
5-Propyl-resorcinol	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-propyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	55	38
4-Butyl-resorcinol	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	$POCl_3$	7-Hydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methyl-6-butyl-coumarin	—	188
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methyl-6-butyl-coumarin-3-acetate	—	181
5-Butyl-resorcinol	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-butyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	59	38
2-Isoamyl-resorcinol (tetrahydro-tubanol)	Malic acid	H_2SO_4	7-Hydroxy-8-isoamylcoumarin	39	189
	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-8-isoamyl-coumarin	20	169
	Ethyl 3-hydroxy-7-methoxy-3-chromene-4-carboxylate	HCl	7-Hydroxy-7'-methoxy-8-isoamyl-chromeno-(3',4',4,3)-coumarin	—	99
	Ethyl 3-hydroxy-8-methoxy-3-chromene-4-carboxylate	HCl	7-Hydroxy-8'-methoxy-8-isoamyl-chromeno-(3',4',4,3)-coumarin	49	99
	Ethyl 3-hydroxy-6,7-dimethoxy-3-chromene-4-carboxylate	H_2SO_4 (85%)	7-Hydroxy-6',7'-dimethoxy-8-isoamylchromeno-(3',4',4,3)-coumarin	—	99
2-Isoamyl-resorcinol monomethyl ether	Malic acid	H_2SO_4	7-Methoxy-8-isoamylcoumarin	66	190, 191
4-Isoamyl-resorcinol	Malic acid	H_2SO_4	7-Hydroxy-6-isoamylcoumarin	—	192
	Ethyl acetoacetate	H_2SO_4; $POCl_3$; $AlCl_3$	7-Hydroxy-4-methyl-6-isoamyl-coumarin	—	30

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

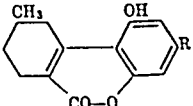| Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
5-Amyl-resorcinol (olivetol)	Ethyl acetoacetate	H_2SO_4	5-Hydroxy-4-methyl-7-amylcoumarin	—	36
	Ethyl acetoacetate	$POCl_3$	5-Hydroxy-4-methyl-7-amylcoumarin	85	182, 193
	Ethyl α-butylacetoacetate	$POCl_3$	5-Hydroxy-3-butyl-4-methyl-7-amylcoumarin	60	182, 193
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4	5-Hydroxy-7-amyl-3,4-cyclopentenocoumarin	—	36
	Ethyl cyclohexanone-2-carboxylate	H_2SO_4	5-Hydroxy-7-amyl-3,4-cyclohexenocoumarin	—	36
	Ethyl cyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-7,8,9,10-tetrahydro-6-dibenzopyrone	82	93
	Ethyl 4-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-8-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	76	93
	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	5-Hydroxy-5'-methyl-7-amyl-3,4-cyclohexenocoumarin	91	9
	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	57–75	93, 194
	Ethyl 5-ethylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-9-ethyl-7,8,9,10-tetrahydro-6-dibenzopyrone	46	98
	Ethyl 6-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-10-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	—	93
	Ethyl 3,5-dimethylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-7,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone	63	98
	Ethyl 4,5-dimethylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-8,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone	61	98
	Ethyl 5,5-dimethylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-amyl-9,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone	33	98
	Ethyl cycloheptanone-2-carboxylate	$POCl_3$	5-Hydroxy-7-amyl-3,4-pentamethylenecoumarin	45	98
5-Isoamyl-resorcinol	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	5-Hydroxy-5'-methyl-7-isoamyl-3,4-cyclohexenocoumarin	—	37
4-Hexyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (82%)	7-Hydroxy-4-methyl-6-hexylcoumarin	39	195
5-Hexyl-resorcinol	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-hexyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	52	38
5-Isohexyl-resorcinol	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	5-Hydroxy-5'-methyl-7-isohexyl-3,4-cyclohexenocoumarin	—	37
5-Heptyl-resorcinol	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-heptyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	59	38
5-Octyl-resorcinol	Ethyl 5-methylcyclohexanone-2-carboxylate	$POCl_3$	1-Hydroxy-3-octyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone	59	38
4-Dodecyl-resorcinol	Ethyl acetoacetate	H_2SO_4; $POCl_3$; $AlCl_3$	7-Hydroxy-4-methyl-6-dodecylcoumarin	—	30

Note: References 142–244 are listed on pp. 57–58

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Hexadecyl-resorcinol	Ethyl acetoacetate	H_2SO_4; $POCl_3$; $AlCl_3$	7-Hydroxy-4-methyl-6-hexadecyl-coumarin	—	30
4-Octadecyl-resorcinol	Ethyl acetoacetate	$POCl_3$	7-Hydroxy-4-methyl-6-octadecyl-coumarin	—	196

Miscellaneous C-Alkylresorcinols

| 5-Alkyl-resorcinol | Ethyl 5-methylcyclohexa-none-2-carboxylate | $POCl_3$ | 1-Hydroxy-3-alkyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzo-pyrone | | |

R = alkyl group

5-Alkyl substituent			3-Alkyl substituent		
1-Methyl-butyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-Methylbutyl	70	197
1-Ethylbutyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-Ethylbutyl	73	197
1-Methyl-pentyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-Methylpentyl	53	197
1-n-Propyl-pentyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-n-Propylpentyl	51	197
1-Methyl-hexyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-Methylhexyl	47	197
1-Methyl-heptyl	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	1-Methylheptyl	62	197
$-CH(CH_3)(CH_2)_6CH_3$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH(CH_3)(CH_2)_6CH_3$	38	198
$-CH(CH_3)(CH_2)_7CH_3$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH(CH_3)(CH_2)_7CH_3$	41	198
$-CH_2CH(CH_3)CH_2CH_3$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH_2CH(CH_3)CH_2CH_2CH_3$	60	198
$-CH_2CH_2CH(CH_3)CH_2CH_3$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH_2CH_2CH(CH_3)CH_2CH_3$	72	198
$-CH_2CH_2CH_2CH(CH_3)_2$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH_2CH_2CH_2CH(CH_3)_2$	73	198
$-C(CH_3)_2C_3H_7$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-C(CH_3)_2C_3H_7$	73	199
$-C(CH_3)CH(CH_3)C_2H_5$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-C(CH_3)CH(CH_3)C_2H_5$	30	199
$-CH(C_2H_5)CH(CH_3)CH_3$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH(C_2H_5)CH(CH_3)CH_3$	28	199
$-C(CH_3)_2C_6H_{13}$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-C(CH_3)_2C_6H_{13}$	37	199
$-CH(CH_3)CH(CH_3)C_6H_{11}$	Ethyl 5-methylcyclohexa-none-2-carboxylate	$POCl_3$	$-CH(CH_3)CH(CH_3)C_6H_{11}$	24	199

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
β-Resorcylic acid	Malic acid	H_2SO_4	7-Hydroxycoumarin-6-carboxylic acid	30	45, 200, 201
	Malic acid	H_2SO_4	7-Hydroxycoumarin-6-carboxylic acid (isolated as methyl 7-methoxycoumarin-6-carboxylate)	20	120
			5-Hydroxycoumarin-6-carboxylic acid (isolated as methyl 5-methoxycoumarin-6-carboxylate)	1	
	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methylcoumarin-6-carboxylic acid	21	45
			7-Hydroxy-4-methylcoumarin	Traces	
	Ethyl acetoacetate	$AlCl_3$	5-Hydroxy-4-methylcoumarin-6-carboxylic acid	14	53
	Ethyl 4-methylcyclopentanone-2-carboxylate	H_2SO_4 (73%)	7-Hydroxy-6-carboxy-3,4-(4'-methylcyclopenteno)coumarin	—	48
	Ethyl cyclohexanone-2-carboxylate	H_2SO_4 (73%)	7-Hydroxy-6-carboxy-3,4-cyclohexenocoumarin	—	48
Methyl β-resorcylate	Malic acid	H_2SO_4	7-Hydroxycoumarin-6-carboxylic acid	—	45
	Ethyl acetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	43	45
			7-Hydroxy-4-methylcoumarin-6-carboxylic acid	31	
	Ethyl acetoacetate	P_2O_5	Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	3	45
	Ethyl acetoacetate	$POCl_3$	Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	5	45
	Ethyl acetoacetate	$AlCl_3$	Methyl 5-hydroxy-4-methylcoumarin-6-carboxylate	18	53
			Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	2	
	Ethyl acetoacetate	HCl	Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	19	45
	Ethyl acetoacetate	$ZnCl_2$	Methyl 5-hydroxy-4-methylcoumarin-6-carboxylate	—	53
			Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	—	
	Ethyl α-chloroacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3-chloro-4-methylcoumarin-6-carboxylate	6	46
	Ethyl α-methylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3,4-dimethylcoumarin-6-carboxylate	20	47
			7-Hydroxy-3,4-dimethylcoumarin-6-carboxylic acid	7	
	Ethyl α-ethylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3-ethyl-4-methylcoumarin-6-carboxylate	—	47
	Ethyl α-propylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3-propyl-4-methylcoumarin-6-carboxylate	—	47
			7-Hydroxy-3-propyl-4-methylcoumarin-6-carboxylic acid	—	
	Ethyl α-butylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3-butyl-4-methylcoumarin-6-carboxylate	—	47
			7-Hydroxy-3-butyl-4-methylcoumarin-6-carboxylic acid	—	
	Ethyl α-benzylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-3-benzyl-4-methylcoumarin-6-carboxylate	—	47

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Methyl β-resorcylate (Cont'd)	Diethyl acetosuccinate	H_2SO_4 (80%)	Methyl 7-hydroxy-4-methyl-coumarin-6-carboxylate ¶¶	54	42
	Ethyl α-benzoylacetoacetate	H_2SO_4 (80%)	Methyl 7-hydroxy-4-phenylcoumarin-6-carboxylate *	6	46
			7-Hydroxy-4-phenylcoumarin-6-carboxylic acid *	2	
	Diethyl acetonedicarboxylate	H_2SO_4 (80%)	Ethyl 7-hydroxy-6-carbomethoxy-coumarin-4-acetate	8	46
			7-Hydroxy-6-carbomethoxycoumarin-4-acetic acid	12	
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4 (73%)	7-Hydroxy-6-carbomethoxy-3,4-cyclopentenocoumarin	42	48
	Ethyl 4-methylcyclopentanone-2-carboxylate	H_2SO_4 (73%)	7-Hydroxy-6-carbomethoxy-3,4-(4'-methylcyclopenteno)coumarin	46	48
	Ethyl cyclohexanone-2-carboxylate	H_2SO_4 (73%)	7-Hydroxy-6-carbomethoxy-3,4-cyclohexenocoumarin	61	48
	Ethyl cyclohexanone-2-carboxylate	$POCl_3$	7-Hydroxy-6-carbomethoxy-3,4-cyclohexenocoumarin	77	48
	Ethyl cyclohexanone-2-carboxylate	$AlCl_3$	7-Hydroxy-6-carbomethoxy-3,4-cyclohexenocoumarin	77	48
γ-Resorcylic acid	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methylcoumarin-8-carboxylic acid	60	49
2-Acetyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (78%)	7-Hydroxy-4-methyl-8-acetyl-coumarin	46	17
	Ethyl acetoacetate	$AlCl_3$	7-Hydroxy-4-methyl-8-acetylcoumarin	74	17
	Ethyl acetoacetate	$FeCl_3$	7-Hydroxy-4-methyl-8-acetylcoumarin	—	128
	Diethyl acetosuccinate	H_2SO_4 (80%)	7-Hydroxy-4-methyl-8-acetylcoumarin-3-acetic acid	—	42
	Diethyl acetosuccinate	$POCl_3$	Ethyl 7-hydroxy-4-methyl-8-acetyl-coumarin-3-acetate	—	42
4-Acetyl-resorcinol (resacetophenone)	Malic acid	H_2SO_4	7-Hydroxycoumarin *	—	202
	Ethyl acetoacetate	$POCl_3$	7-Hydroxy-4-methyl-6-acetyl-coumarin	40	203
	Ethyl acetoacetate	$POCl_3$	7-Hydroxy-4-methyl-6-acetyl-coumarin	40	12
			5-Hydroxy-4-methyl-6-acetyl-coumarin	—	
	Ethyl acetoacetate	$AlCl_3$	5-Hydroxy-4-methyl-6-acetyl-coumarin	37–41	53
	Ethyl α-methylacetoacetate	$AlCl_3$	5-Hydroxy-3,4-dimethyl-6-acetyl-coumarin	7	116
	Ethyl α-ethylacetoacetate	$AlCl_3$	5-Hydroxy-3-ethyl-4-methyl-6-acetylcoumarin	—	116
	Ethyl α-benzylacetoacetate	$AlCl_3$	5-Hydroxy-3-benzyl-4-methyl-6-acetylcoumarin	—	116
	Ethyl cyclopentanone-2-carboxylate	$POCl_3$	7-Hydroxy-6-acetyl-3,4-cyclopentenocoumarin	25	48
	Ethyl cyclopentanone-2-carboxylate	$AlCl_3$	5-Hydroxy-6-acetyl-3,4-cyclopentenocoumarin	—	48
	Ethyl 4-methylcyclopentanone-2-carboxylate	$AlCl_3$	5-Hydroxy-6-acetyl-3,4-(4'-methylcyclopenteno)coumarin	—	48

Note: References 142–244 are listed on pp. 57–58.

¶¶ In this condensation a —$CH_2CO_2C_2H_5$ group was eliminated.

* In this condensation an acetyl group was eliminated.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Acetyl-resorcinol (resaceto-phenone) (Cont'd)	Ethyl cyclohexanone-2-carboxylate	POCl₃	7-Hydroxy-6-acetylcyclohexeno-(1′,2′,4,3)-coumarin	—	96
	Ethyl cyclohexanone-2-carboxylate	AlCl₃	5-Hydroxy-6-acetyl-3,4-cyclohexenocoumarin	82	48
	Ethyl 4-methylcyclohexanone-2-carboxylate	POCl₃	7-Hydroxy-4′-methyl-6-acetyl-cyclohexeno-(1′,2′,4,3)-coumarin	—	96
	Ethyl 5-methylcyclohexanone-2-carboxylate	POCl₃	7-Hydroxy-5′-methyl-6-acetyl-cyclohexeno-(1′,2′,4,3)-coumarin	—	96
	Ethyl trans-β-decalone-3-carboxylate	POCl₃	7-Hydroxy-6-acetyl-trans-octalino-(2′,3′,4,3)-coumarin	—	96
ω-Chloro-resaceto-phenone	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-6-chloroaceto-coumarin	9	126
	Ethyl acetoacetate	HCl	7-Hydroxy-4-methyl-6-chloroaceto-coumarin	4	126
	Diethyl oxalacetate	ZnCl₂ + HCl	7-Hydroxy-4-carbethoxy-6-chloro-acetocoumarin	45	126
2-Propionyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-propionyl-coumarin	—	204
4-Propionyl-resorcinol	Ethyl acetoacetate	POCl₃	7-Hydroxy-4-methyl-6-propionyl-coumarin	25	12
	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-propionyl-coumarin	24	114
2-Butyryl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-butyryl-coumarin	—	205
4-Butyryl-resorcinol	Ethyl acetoacetate	POCl₃	7-Hydroxy-4-methyl-6-butyryl-coumarin	30	12
	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-butyryl-coumarin	37	114
4-Isovaleryl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-isovaleryl-coumarin	45	115
4-Lauroyl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-lauroyl-coumarin	27	115
4-Palmitoyl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-palmitoyl-coumarin	84	115
4-Stearoyl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-stearoyl-coumarin	33	196
2-Benzoyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-benzoyl-coumarin	—	54
	Diethyl acetosuccinate	POCl₃	Ethyl 7-hydroxy-4-methyl-8-benzoylcoumarin-3-acetate	—	42
4-Benzoyl-resorcinol	Ethyl acetoacetate	POCl₃	7-Hydroxy-4-methyl-6-benzoyl-coumarin	10	12
	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-benzoyl-coumarin	—	17
2-o-Toluyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-o-toluyl-coumarin	—	205
2-p-Toluyl-resorcinol	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4-methyl-8-p-toluyl-coumarin	—	204
4-p-Toluyl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-p-toluyl-coumarin	55	114
4-Phenyl-acetyl-resorcinol	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-6-phenyl-acetylcoumarin	42	114
4-Chloro-5-methyl-resorcinol	Ethyl acetoacetate	H₂SO₄; P₂O₅	5-Hydroxy-6-chloro-4,7-dimethyl-coumarin	—	43
	Ethyl α-methylacetoacetate	H₂SO₄; P₂O₅	5-Hydroxy-6-chloro-3,4,7-tri-methylcoumarin	—	43

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Chloro-5-methyl-resorcinol (*Cont'd*)	Ethyl α-ethylacetoacetate	H_2SO_4; P_2O_5	5-Hydroxy-6-chloro-3-ethyl-4,7-dimethylcoumarin	—	43
	Citric acid	H_2SO_4	5-Hydroxy-6-chloro-7-methylcoumarin-4-acetic acid	—	43
4-Chloro-6-ethyl-resorcinol	Ethyl acetoacetate	H_2SO_4; P_2O_5	5-Hydroxy-4-methyl-6(or 8)-chloro-8-(or 6)-ethylcoumarin	—	185
	Ethyl α-methylacetoacetate	H_2SO_4	5-Hydroxy-3,4-dimethyl-6(or 8)-chloro-8(or 6)-ethylcoumarin	—	185
4-Bromo-5-methyl-resorcinol	Ethyl acetoacetate	H_2SO_4; P_2O_5	5-Hydroxy-6-bromo-4,7-dimethylcoumarin	—	43
	Ethyl α-methylacetoacetate	H_2SO_4	5-Hydroxy-6-bromo-3,4,7-trimethylcoumarin	—	43
4-Chloro-6-propionyl-resorcinol	Ethyl acetoacetate	H_2SO_4	5-Hydroxy-4-methyl-6(or 8)-chloro-8(or 6)-propionylcoumarin	—	185
6-Bromo-4-acetyl-resorcinol	Ethyl acetoacetate	$AlCl_3$	5-Hydroxy-4-methyl-6-acetyl-8-bromocoumarin	16	117
4,6-Dimethyl-resorcinol	Ethyl acetoacetate	H_2SO_4	5-Hydroxy-4,6,8-trimethylcoumarin	—	206
2-Methyl-4-ethyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (80%)	7-Hydroxy-4,8-dimethyl-6-ethylcoumarin	—	22
2-Methyl-4-propyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (80%)	7-Hydroxy-4,8-dimethyl-6-propylcoumarin	—	23
2-Ethyl-4-methyl-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4,6-dimethyl-8-ethylcoumarin	90	180
2-Ethyl-5 methyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (73%)	7-Hydroxy-4,5-dimethyl-8-ethylcoumarin	70	207
	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3,4,5-trimethyl-8-ethylcoumarin	—	207
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3,8-diethyl-4,5-dimethylcoumarin	—	207
	Ethyl α-propylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3-propyl-4,5-dimethyl-8-ethylcoumarin	—	207
2,4-Diethyl-resorcinol	Ethyl acetoacetate	H_2SO_4; C_2H_5ONa	7-Hydroxy-4-methyl-6,8-diethylcoumarin	—	208
4-Ethyl-5-methyl-resorcinol	Malic acid	H_2SO_4 (85%)	7-Hydroxy-5-methyl-6-ethylcoumarin	50	209
	Ethyl acetoacetate	H_2SO_4 (85%)	5-Hydroxy-4,7-dimethyl-6-ethylcoumarin	60	209
4,6-Diethyl-resorcinol	Malic acid	H_2SO_4 (75%)	5-Hydroxy-6,8-diethylcoumarin	—	210
	Ethyl acetoacetate	H_2SO_4 (75%)	5-Hydroxy-4-methyl-6,8-diethylcoumarin	—	210
	Ethyl cyclopentanone-2-carboxylate	$POCl_3$	5-Hydroxy-6,8-diethylcyclopenteno-(1',2',4,3)-coumarin	38	91
	Ethyl 4-methylcyclopentanone-2-carboxylate	$POCl_3$	5-Hydroxy-6,8-diethyl-4'-methyl-cyclopenteno-(1',2',4,3)-coumarin	—	91
2-Propyl-5-methyl-resorcinol	Ethyl acetoacetate	H_2SO_4 (73%)	7-Hydroxy-4,5-dimethyl-8-propylcoumarin	—	207
	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3,4,5-trimethyl-8-propylcoumarin	—	207

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

Condensations with Dihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
2-Propyl-5-methyl-resorcinol (*Cont'd*)	Ethyl α-ethylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3-ethyl-4,5-dimethyl-8-propylcoumarin	—	207
	Ethyl α-propylacetoacetate	H₂SO₄ (73%)	7-Hydroxy-3,8-dipropyl-4,5-di-methylcoumarin	—	207
2,4-Dihydroxy-5-ethyl-benzoic acid	Ethyl acetoacetate	H₂SO₄	5-Hydroxy-4-methyl-8-ethylcoumarin-6-carboxylic acid	15	211
	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4-methyl-8-ethylcoumarin-6-carboxylic acid	24	211
Methyl 2,4-dihydroxy-5-ethyl-benzoate	Ethyl acetoacetate	H₂SO₄ (73%)	Methyl 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylate	38	12
	Ethyl acetoacetate	H₂SO₄ (80%)	Methyl 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylate	22	211
	Ethyl acetoacetate	AlCl₃	Methyl 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylate	49	211
5-Methyl-resorcinol-2-carboxylic acid (*p*-or-sellinic acid)	Ethyl acetoacetate	H₂SO₄	7-Hydroxy-4,5-dimethylcoumarin-8-carboxylic acid	32	212
Ethyl 5-methyl-resorcinol-6-carboxylate	Malic acid	H₂SO₄	5-Hydroxy-7-methylcoumarin †	67	213
	Ethyl acetoacetate	H₂SO₄	Ethyl 5-hydroxy-4,7-dimethyl-coumarin-6-carboxylate	60	213
	Ethyl acetoacetate	AlCl₃	Ethyl 5-hydroxy-4,7-dimethyl-coumarin-6-carboxylate	30	213
2,4-Dihydroxy-3-isoamyl-benzoic acid	Malic acid	H₂SO₄	7-Hydroxy-8-isoamylcoumarin-6-carboxylic acid	41	189
5-Methyl-2-acetyl-resorcinol (γ-orca-ceto-phenone)	Ethyl acetoacetate	H₂SO₄; H₂SO₄ (73%); POCl₃	5-Hydroxy-4,7-dimethylcoumarin ‡	—	214
5-Methyl-6-acetyl-resorcinol (β-orcaceto-phenone)	Ethyl acetoacetate	H₂SO₄	5-Hydroxy-4,7-dimethylcoumarin ‡	—	17
	Ethyl acetoacetate	POCl₃	5-Hydroxy-4,7-dimethyl-6-acetyl-coumarin	18	12
	Ethyl acetoacetate	AlCl₃	5-Hydroxy-4,7-dimethyl-6-acetyl-coumarin	—	17
5-Methyl-2-propionyl-resorcinol	Ethyl acetoacetate	H₂SO₄	5-Hydroxy-4,7-dimethylcoumarin ‡ 5-Hydroxy-4,7-dimethylcoumarin §	— —	215
5-Methyl-2-butyryl-resorcinol	Ethyl acetoacetate	H₂SO₄	5-Hydroxy-4,7-dimethylcoumarin ‖	—	215
2-Ethyl-4-acetyl-resorcinol	Ethyl acetoacetate	POCl₃	7-Hydroxy-4-methyl-6-acetyl-8-ethylcoumarin	24	184

Note: References 142–244 are listed on pp. 57–58.

† A carbethoxyl group was eliminated in the condensation.

‡ An acetyl group was eliminated in the condensation.

§ A propionyl group was eliminated in the condensation.

‖ A butyryl group was eliminated in the condensation.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Ethyl-2-acetyl-resorcinol	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3,4-dimethyl-6-ethyl-8-acetylcoumarin	75	55
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3,6-diethyl-4-methyl-8-acetylcoumarin	70	55
	Ethyl α-propylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3-propyl-4-methyl-6-ethyl-8-acetylcoumarin	70	55
	Ethyl α-butylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3-butyl-4-methyl-6-ethyl-8-acetylcoumarin	—	55
	Ethyl α-allylacetoacetate	H_2SO_4 (73%)	7-Hydroxy-3-allyl-4-methyl-6-ethyl-8-acetylcoumarin	50	55
	Ethyl benzoylacetate	H_2SO_4 (73%)	7-Hydroxy-4-phenyl-6-ethyl-8-acetylcoumarin	80	55
4-Ethyl-6-acetyl-resorcinol	Ethyl acetoacetate	$POCl_3$	5-Hydroxy-4-methyl-6-acetyl-8-ethylcoumarin	—	12
	Ethyl acetoacetate	$AlCl_3$	5-Hydroxy-4-methyl-6-acetyl-8-ethylcoumarin	39	117
4-Ethyl-2-benzoyl-resorcinol	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-4-methyl-6-ethyl-8-benzoylcoumarin	—	216
	Ethyl acetoacetate	H_2SO_4 (73%)	7-Hydroxy-4-methyl-6-ethyl-8-benzoylcoumarin	66	207
2,4-Diethyl-5-methyl-resorcinol	Ethyl acetoacetate	$AlCl_3$	7-Hydroxy-4,5-dimethyl-6,8-di-ethylcoumarin	—	207
4,6-Diethyl-5-methyl-resorcinol	Malic acid	H_2SO_4 (85%)	5-Hydroxy-6,8-diethyl-7-methyl-coumarin	—	209
	Ethyl acetoacetate	H_2SO_4 (85%)	5-Hydroxy-4,7-dimethyl-6,8-di-ethylcoumarin	—	209
Hydroquinone	Malic acid	H_2SO_4	6-Hydroxycoumarin	Poor	39
	Ethyl acetoacetate	H_2SO_4	6-Hydroxy-4-methylcoumarin	20–34	148, 217
	Ethyl α-methylacetoacetate	H_2SO_4	6-Hydroxy-3,4-dimethylcoumarin	3	108, 217
	Ethyl α-methylacetoacetate	P_2O_5	6-Hydroxy-2,3-dimethylchromone	30	4
	Ethyl α-ethylacetoacetate	$AlCl_3$	6-Hydroxy-3-ethyl-4-methylcou-marin	—	207
	Diethyl acetonedicarboxylate	H_2SO_4	Ethyl 6-hydroxycoumarin-4-acetate	Poor	26
	Diethyl oxalacetate	H_2SO_4	Ethyl 6-hydroxycoumarin-4-car-boxylate	—	89
	Ethyl cyclohexanone-2-car-boxylate	H_2SO_4	6-Hydroxy-3,4-cyclohexenocou-marin	10	9
	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	6-Hydroxy-5'-methyl-3,4-cyclo-hexenocoumarin	2	9
Hydro-quinone diacetate	Ethyl acetoacetate	H_2SO_4 (73%)	6-Hydroxy-4-methylcoumarin	30	56
Hydro-quinone mono-methyl ether	Ethyl α-methylacetoacetate	H_2SO_4	6-Methoxy-3,4-dimethylcoumarin	Poor	218
2-Chlorohy-droquinone	Ethyl acetoacetate	H_2SO_4 (73%)	6-Hydroxy-4-methyl-7-chlorocou-marin	20	56
2-Methylhy-droquinone	Malic acid	H_2SO_4 (85%)	6-Hydroxy-7-methylcoumarin	45	219
	Ethyl acetoacetate	H_2SO_4 (73%)	6-Hydroxy-4,7-dimethylcoumarin	70	56
	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3,4,7-trimethylcou-marin	45	56
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3-ethyl-4,7-dimethyl-coumarin	25	56

Note: References 142–244 are listed on pp. 57–58.

TABLE II—*Continued*

CONDENSATIONS WITH DIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
2-Methylhydroquinone (*Cont'd*)	Ethyl α-propylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3-propyl-4,7-dimethylcoumarin	20	56
	Ethyl benzoylacetate	H_2SO_4 (73%)	6-Hydroxy-4-phenyl-7-methylcoumarin	45	56
2-Ethylhydroquinone	Ethyl acetoacetate	H_2SO_4 (73%)	6-Hydroxy-4-methyl-7-ethylcoumarin	45	56
	Ethyl α-methylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3,4-dimethyl-7-ethylcoumarin	40	56
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3,7-diethyl-4-methylcoumarin	35	56
	Ethyl α-propylacetoacetate	H_2SO_4 (73%)	6-Hydroxy-3-propyl-4-methyl-7-ethylcoumarin	5-10	56
	Ethyl benzoylacetate	H_2SO_4 (73%)	6-Hydroxy-4-phenyl-7-ethylcoumarin	15	56
2-Amylhydroquinone	Ethyl 1-methylcyclohexan-3-one-4-carboxylate	H_2SO_4	6-Hydroxy-5'-methyl-7-amyl-3,4-cyclohexenocoumarin	—	36
Trimethylhydroquinone	Ethyl acetoacetate	P_2O_5	6-Hydroxy-2,5,7,8-tetramethylchromone	17	220, 221
	Ethyl α-methylacetoacetate	P_2O_5	6-Hydroxy-2,3,5,7,8-pentamethylchromone	19	221

Note: References 142–244 are listed on pp. 57–58.

TABLE III

CONDENSATIONS WITH TRIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Pyrogallol	Malic acid	H_2SO_4	7,8-Dihydroxycoumarin	—	1
	Ethyl acetoacetate	H_2SO_4	7,8-Dihydroxy-4-methylcoumarin	—	2
	Ethyl acetoacetate	P_2O_5	7,8-Dihydroxy-4-methylcoumarin	32	33, 107
	Ethyl acetoacetate	H_3PO_4	7,8-Dihydroxy-4-methylcoumarin	—	127
	Ethyl acetoacetate	$FeCl_3$; $TiCl_4$	7,8-Dihydroxy-4-methylcoumarin	—	128
	Ethyl acetoacetate	$SnCl_4$	7,8-Dihydroxy-4-methylcoumarin	Quant.	128
	Ethyl α-chloroacetoacetate	H_2SO_4	7,8-Dihydroxy-3-chloro-4-methylcoumarin	50	32
	Ethyl α-chloroacetoacetate	P_2O_5	7,8-Dihydroxy-3-chloro-4-methylcoumarin	—	33
	Ethyl α-methylacetoacetate	H_2SO_4	7,8-Dihydroxy-3,4-dimethylcoumarin	31	107
	Ethyl α-methylacetoacetate	P_2O_5	7,8-Dihydroxy-3,4-dimethylcoumarin	Poor	33, 107
	Ethyl α-ethylacetoacetate	H_2SO_4	7,8-Dihydroxy-3-ethyl-4-methylcoumarin	—	33
	Ethyl α-allylacetoacetate	$POCl_3$	7,8-Dihydroxy-3-allyl-4-methylcoumarin	63	70
	Ethyl α-allylacetoacetate	HCl	7,8-Dihydroxy-3-(β-chloropropyl)-4-methylcoumarin	47	124
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	H_2SO_4 (78%)	7,8-Dihydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methylcoumarin	26	72
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	$POCl_3$	7,8-Dihydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methylcoumarin	Quant	72

Note: References 142–244 are listed on pp. 57–58.

TABLE III—*Continued*

CONDENSATIONS WITH TRIHYDRIC PHENOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
2,4-Dihydroxyanisole	Ethyl acetoacetate	H_2SO_4	7-Hydroxy-6-methoxy-4-methylcoumarin	—	226
Hydroxyhydroquinone triacetate	Malic acid	H_2SO_4 (97%)	6,7-Dihydroxycoumarin	30	227
	Ethyl acetoacetate	H_2SO_4 (73–75%)	6,7-Dihydroxy-4-methylcoumarin	92	60, 219
	Diethyl oxalacetate	$ZnCl_2$	Ethyl 6,7-dihydroxycoumarin-4-carboxylate	—	24
	Ethyl hydroxymethylene phenylacetate	H_2SO_4 (80%)	6,7-Dihydroxy-3-phenylcoumarin	—	228
Phloroglucinol	Ethyl acetoacetate	H_2SO_4	5,7-Dihydroxy-4-methylcoumarin	—	229
	Ethyl acetoacetate (3 moles)	H_2SO_4	Trimethyltricoumarin	10	170
	Ethyl acetoacetate	P_2O_5	5,7-Dihydroxy-4-methylcoumarin	—	101
	Ethyl acetoacetate	H_3PO_4	5,7-Dihydroxy-4-methylcoumarin	—	127
	Ethyl acetoacetate	$FeCl_3$	5,7-Dihydroxy-4-methylcoumarin	66	128
	Ethyl acetoacetate	$SnCl_4$	5,7-Dihydroxy-4-methylcoumarin	78	128
	Ethyl α-chloroacetoacetate	H_2SO_4	5,7-Dihydroxy-3-chloro-4-methylcoumarin	37	26
	Ethyl α-chloroacetoacetate	P_2O_5	5,7-Dihydroxy-3-chloro-4-methylcoumarin	—	33
	Ethyl α-methylacetoacetate	H_2SO_4 (75%); P_2O_5	5,7-Dihydroxy-3,4-dimethylcoumarin	—	101
	Ethyl α-ethylacetoacetate	H_2SO_4 (73%); P_2O_5	5,7-Dihydroxy-3-ethyl-4-methylcoumarin	46	101
	Ethyl α-allylacetoacetate	H_2SO_4	5,7-Dihydroxy-3-allyl-4-methylcoumarin	72	70
	Ethyl α-allylacetoacetate	HCl	5,7-Dihydroxy-4-methyl-3-(β-chloropropyl)coumarin	—	124
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	P_2O_5	5,7-Dihydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methylcoumarin	Poor	72
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	$POCl_3$	5,7-Dihydroxy-3-(α-hydroxy-β,β,β-trichloroethyl)-4-methylcoumarin	29	72
	Ethyl α-phenylacetoacetate	$ZnCl_2$	5,7-Dihydroxy-3-phenyl-4-methylcoumarin	—	105
	Ethyl α-benzylacetoacetate	H_2SO_4	5,7-Dihydroxy-3-benzyl-4-methylcoumarin	—	105
	Ethyl α-benzylacetoacetate	$POCl_3$	5,7-Dihydroxy-3-benzyl-4-methylcoumarin	—	172
	Ethyl α-o-carboxybenzyl-acetoacetate	HCl	5,7-Dihydroxy-3-o-carboxybenzyl-4-methylcoumarin	Good	79
	Diethyl acetosuccinate	H_2SO_4	Ethyl 5,7-dihydroxy-4-methylcoumarin-3-acetate	—	179
	Diethyl acetosuccinate	H_2SO_4 (80%)	5,7-Dihydroxy-4-methylcoumarin	—	34
	Diethyl acetosuccinate	$POCl_3$	Ethyl 5,7-dihydroxy-4-methylcoumarin-3-acetate	91	34
	Diethyl α-acetylglutarate	H_2SO_4 (concd. and 78%)	5,7-Dihydroxy-4-methylcoumarin-3-propionic acid	32	77
	Ethyl phthalylacetoacetate	HCl	5,7-Dihydroxy-4-methylcoumarin-3-benzoyl-o-carboxylic acid	—	79
	Acetonedicarboxylic acid	H_2SO_4	5,7-Dihydroxycoumarin-4-acetic acid	—	26
	Ethyl butyroacetate	H_2SO_4 (75%)	5,7-Dihydroxy-4-propylcoumarin	—	35

TABLE III—*Continued*

Condensations with Trihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Phloroglucinol (*Cont'd*)	Ethyl benzoylacetate	P_2O_5	5,7-Dihydroxy-4-phenylcoumarin	—	101
	Ethyl benzoylacetate	$ZnCl_2$	5,7-Dihydroxy-4-phenylcoumarin	—	222
	Ethyl α-benzylbenzoylacetate	$ZnCl_2$	5,7-Dihydroxy-3-benzyl-4-phenyl-coumarin	85–90	105
	Ethyl 3,4,5-trimethoxy-benzoylacetate	H_2SO_4 (73%)	5,7-Dihydroxy-4-(3',4',5'-trimeth-oxyphenyl)coumarin	—	223
	Ethyl γ-phenylacetoacetate	H_2SO_4 (concd. and 80%)	5,7-Dihydroxy-4-benzylcoumarin	—	80, 81
	Ethyl cyclopentanone-2-carboxylate	$POCl_3$	5,7-Dihydroxycyclopenteno-(1',2',4,3)-coumarin	55	91
	Ethyl 4-methylcyclopenta-none-2-carboxylate	$POCl_3$	5,7-Dihydroxy-4'-methylcyclo-penteno-(1',2',4,3)-coumarin	—	91
	Ethyl cyclohexanone-2-carboxylate	$POCl_3$	5,7-Dihydroxycyclohexeno-(1',2',4,3)-coumarin	—	124
	Ethyl 4-methylcyclohexa-none-2-carboxylate	$POCl_3$	5,7-Dihydroxy-4'-methylcyclo-hexeno-(1',2',4,3)-coumarin	—	97
	Ethyl 5-methylcyclohexa-none-2-carboxylate	H_2SO_4; $POCl_3$	5,7-Dihydroxy-5'-methylcyclo-hexeno-(1',2',4,3)-coumarin	—	97
	Ethyl 5-methylcyclohexa-none-2-carboxylate	$ZnCl_2$	3,4-Tetrahydro-4'-methylbenzo-5,7-*dihydroxycoumarin*	75–80	94
	Ethyl 6-methylcyclohexa-none-2-carboxylate	$POCl_3$	5,7-Dihydroxy-6'-methylcyclo-hexeno-(1',2',4,3)-coumarin	—	97
	Ethyl *trans*-β-decalone-3-carboxylate	H_2SO_4	5,7-Dihydroxy-*trans*-octalino-(2',3',4,3)-coumarin	—	97
	Ethyl β-coumaranone-2-car-boxylate	HCl	5,7-Dihydroxycoumarono-(2',3',3,4)-coumarin	—	100
	Ethyl 5-methyl-β-coumara-none-2-carboxylate	HCl	5,7-Dihydroxy-5'-methylcoumarono-(2',3',3,4)-coumarin	—	100
	Ethyl 6-methoxy-β-coumara-none-2-carboxylate	HCl	5,7-Dihydroxy-6'-methoxycouma-rono-(2',3',3,4)-coumarin	—	100
	Ethyl 3-hydroxy-7-methoxy-3-chromene-4-carboxylate	HCl	5,7-Dihydroxy-7'-methoxychro-meno-(3',4',4,3)-coumarin	—	99
	Ethyl 3-hydroxy-8-methoxy-3-chromene-4-carboxylate	H_2SO_4 (85%); HCl	5,7-Dihydroxy-8'-methoxychro-meno-(3',4',4,3)-coumarin (impure)	—	99
	Ethyl 3-hydroxy-6,7-dimeth-oxy-3-chromene-4-car-boxylate	H_2SO_4 (85%)	5,7-Dihydroxy-6',7'-dimethoxy-chromeno-(3',4',4,3)-coumarin (impure)	—	99
Phloroglucinol mono-methyl ether	Ethyl acetoacetate	H_3PO_4	5-Hydroxy-7-methoxy-4-methyl-coumarin and 7-hydroxy-5-meth-oxy-4-methylcoumarin	—	230
Phloroglucinol dimethyl ether	Ethyl acetoacetate	P_2O_5	5,7-Dimethoxy-4-methylcoumarin	70	101
	Ethyl acetoacetate	H_3PO_4	5,7-Dimethoxy-4-methylcoumarin	63	230
	Ethyl α-methylacetoacetate	P_2O_5	5,7-Dimethoxy-3,4-dimethylcou-marin	—	101
	Ethyl α-benzylacetoacetate	P_2O_5	5,7-Dimethoxy-3-benzyl-4-methyl-coumarin	18	231
	Ethyl α-p-methoxybenzyl-acetoacetate	P_2O_5	5,7,4'-Trimethoxy-3-benzyl-4-meth-ylcoumarin	11	231
Methyl-phloro-glucinol	Malic acid	H_2SO_4	Isolated as 5,7-dimethoxy-8-methyl-coumarin and 5,7-dimethoxy-6-*methylcoumarin after methyla*-tion	11 2	232

Note: References 142–244 are listed on pp. 57–58.

TABLE III—*Continued*

Condensations with Trihydric Phenols

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Methyl-phloroglucinol (*Cont'd*)	Ethyl acetoacetate	H_2SO_4	5,7-Dihydroxy-4,6-(or 8)-dimethyl-coumarin	95	58
Dimethyl-phloroglucinol	Ethyl acetoacetate	H_2SO_4	5,7-Dihydroxy-4,6,8-trimethyl-coumarin	69	58
Methyl phloroglucinol carboxylate	Ethyl acetoacetate	H_2SO_4 (80%)	Methyl 5,7-dihydroxy-4-methyl-coumarin-6(or 8)-carboxylate	47	59
	Ethyl acetoacetate	$AlCl_3$	Methyl 5,7-dihydroxy-4-methyl-coumarin-6(or 8)-carboxylate	44	59
Phloroacetophenone	Ethyl acetoacetate	H_2SO_4	5,7-Dihydroxy-4-methyl-6(or 8)-acetylcoumarin	18	17
	Ethyl acetoacetate	$AlCl_3$	5,7-Dihydroxy-4-methyl-6(or 8)-acetylcoumarin	18	17
Phlorobenzophenone	Ethyl acetoacetate	H_2SO_4 (85%)	5,7-Dihydroxy-4-methyl-6(or 8)-benzoylcoumarin	—	207

Note: References 142–244 are listed on pp. 57–58.

TABLE IV

Condensations with Naphthols *

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
α-Naphthol	Malic acid	H_2SO_4	α-Naphthacoumarin	—	233
	Ethyl acetoacetate	H_2SO_4	4-Methyl-α-naphthacoumarin	60	233, 234
	Ethyl acetoacetate	H_2SO_4 (80–84%)	4-Methyl-1,2,α-naphthapyrone	85–Quant.	108, 156
	Ethyl acetoacetate	P_2O_5	4-Methyl-1,2,α-naphthapyrone	18	33, 108
	Ethyl acetoacetate	HCl	4-Methyl-1,2,α-naphthapyrone	93	123, 234
	Ethyl acetoacetate	H_3PO_4; CH_3CO_2Na	4-Methyl-1,2,α-naphthapyrone	—	127
	Ethyl α-chloroacetoacetate	H_2SO_4	3-Chloro-4-methyl-1,2,α-naphtha-pyrone	Good	26, 159
	Ethyl α-chloroacetoacetate	P_2O_5	3-Chloro-4-methyl-1,2,α-naphtha-pyrone	—	33
	Ethyl α-methylacetoacetate	H_2SO_4 (concd. or 84%)	3,4-Dimethyl-α-naphthacoumarin	—	33, 75, 108
	Ethyl α-methylacetoacetate	P_2O_5	3,4-Dimethyl-α-naphthacoumarin	33	33, 108
	Ethyl α-ethylacetoacetate	H_2SO_4	3-Ethyl-4-methyl-α-naphthacoumarin	30	233
	Ethyl α-propylacetoacetate	H_2SO_4	3-Propyl-4-methyl-1,2,α-naphthapyrone	—	33
	Ethyl α-isopropylacetoacetate	H_2SO_4	3-Isopropyl-4-methyl-1,2,α-naphthapyrone	—	33

Note: References 142–244 are listed on pp. 57–58.

* The coumarins and chromones derived from naphthols have been called α- or β-naphthacoumarins or α- or β-naphthachromones by various workers. These names are inappropriate as they do not convey the proper idea of the structures of these compounds. The names 1,2,α-naphthapyrone and 1,4,α-naphthapyrone for the coumarins and chromones, respectively, from α-naphthol and 1,2,β,α-naphthapyrone and 1,2,β,β-naphthapyrone for the coumarins from β-naphthol, and 1,4,β,α-naphthapyrone and 1,4,β,β-naphthapyrone for the chromones from β-naphthol as suggested by Dey and Lakshminarayan (ref. 110) are rational. However, in order to avoid confusion, the original names as given by the authors are given in the tables.

TABLE IV—*Continued*

CONDENSATIONS WITH NAPHTHOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
α-Naphthol (*Cont'd*)	Ethyl α-allylacetoacetate	H_2SO_4	3-Allyl-4-methyl-5,6-naphtha-α-pyrone	86	70
	Ethyl α-allylacetoacetate	HCl	3-β-Chloropropyl-4-methyl-5,6,α-naphtha-1,2-pyrone	—	124
	Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate	$POCl_3$	4-Methyl-3-(α-hydroxy-β,β,β-trichloroethyl)-1,2,α-naphthapyrone	25	72
	Ethyl α-phenylacetoacetate	H_2SO_4	3-Phenyl-4-methyl-1,2,α-naphthapyrone †	—	104
	Ethyl α-benzylacetoacetate	H_2SO_4	3-Benzyl-4-methyl-1,2,α-naphthapyrone †	—	102
	Ethyl α-benzylacetoacetate	$POCl_3$	3-Benzyl-4-methyl-1,2,α-naphthapyrone	—	172
	Diethyl acetosuccinate	H_2SO_4	Ethyl 4-methyl-1,2,α-naphthapyrone-3-acetate	24	34, 75, 76
	Diethyl acetosuccinate	H_2SO_4 (80%)	4-Methyl-1,2,α-naphthapyrone-3-acetic acid	—	34
	Diethyl acetosuccinate	P_2O_5	Ethyl 4-methyl-1,2,α-naphthapyrone-3-acetate	—	34
	Diethyl acetosuccinate	$POCl_3$	4-Methyl-1,2,α-naphthapyrone-3-acetic acid	40	34
	Diethyl acetosuccinate	$AlCl_3$	4-Methyl-1,2,α-naphthapyrone-3-acetic acid	—	34
	Diethyl α-acetylglutarate	H_2SO_4	Ethyl 4-methyl-1,2,α-naphthapyrone-3-propionate	27	77
	Diethyl α-acetylglutarate	H_2SO_4 (78%)	4-Methyl-1,2,α-naphthapyrone-3-propionic acid	—	77
	Ethyl γ-bromoacetoacetate	H_2SO_4	4-Bromomethyl-1,2,α-naphthapyrone	13	83
	Acetonedicarboxylic acid	H_2SO_4	1,2,α-Naphthapyrone-4-acetic acid	Good	26
	Diethyl oxalacetate	H_2SO_4	Ethyl α-naphthacoumarin-4-carboxylate	—	233
	Ethyl butyroacetate	H_2SO_4 (75%)	α-Naphtha-4-propyl-α-pyrone	—	35
	Ethyl α-benzylbenzoylacetate	H_2SO_4; $SnCl_4$	3-Benzyl-4-phenyl-1,2,α-naphthapyrone	—	103
	Ethyl γ-phenylacetoacetate	H_2SO_4 (80%)	α-Naphtha-4-benzyl-α-pyrone	—	81
	Ethyl cyclopentanone-2-carboxylate	H_2SO_4	Cyclopenteno-(1',2',4,3)-1,2,α-naphthapyrone	71	91
	Ethyl 4-methylcyclopentanone-2-carboxylate	H_2SO_4	4'-Methylcyclopenteno-(1',2',4,3)-1,2,α-naphthapyrone	—	91
	Ethyl cyclohexanone-2-carboxylate	H_2SO_4	3,4-Tetrahydrobenzonaphthacoumarin	Quant.	94
	Ethyl 4-methylcyclohexanone-2-carboxylate	H_2SO_4	4'-Methylcyclohexeno-(1',2',4,3)-1,2,α-naphthapyrone	—	97
	Ethyl 5-methylcyclohexanone-2-carboxylate	H_2SO_4; $POCl_3$	5'-Methylcyclohexeno-(1',2',4,3)-1,2,α-naphthapyrone	—	97
	Ethyl 6-methylcyclohexanone-2-carboxylate	$POCl_3$	6'-Methylcyclohexeno-(1',2',4,3)-1,2,α-naphthapyrone	—	97
	Ethyl *trans*-β-decalone-3-carboxylate	H_2SO_4	*trans*-Octalino-(2',3',4,3)-1,2,α-naphthapyrone	—	97
4-Chloro-α-naphthol	Malic acid	H_2SO_4	6-Chloro-1,2,α,β-naphthapyrone	—	61
	Ethyl acetoacetate	H_2SO_4	6-Chloro-4-methyl-1,2,α,β-naphthapyrone	91	61

Note: References 142–244 are listed on pp. 57–58.
† The 1,4,α-naphthapyrone structure originally assigned to this compound is incorrect; refs. 105, 106.

TABLE IV—*Continued*

CONDENSATIONS WITH NAPHTHOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
4-Chloro-α-naphthol (*Cont'd*)	Ethyl acetoacetate	P$_2$O$_5$; C$_2$H$_5$ONa; CH$_3$CO$_2$Na	6-Chloro-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-chloroacetoacetate	H$_2$SO$_4$; P$_2$O$_5$	3,6-Dichloro-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-methylacetoacetate	H$_2$SO$_4$	6-Chloro-3,4-dimethyl-1,2,α,β-naphthapyrone	48	61
	Ethyl α-methylacetoacetate	P$_2$O$_5$	6-Chloro-2,3-dimethyl-1,4,α,β-naphthapyrone	—	61
	Ethyl α-ethylacetoacetate	H$_2$SO$_4$	6-Chloro-3-ethyl-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-ethylacetoacetate	P$_2$O$_5$	6-Chloro-2-methyl-3-ethyl-1,4,α,β-naphthapyrone	—	61
	Ethyl α-propylacetoacetate	H$_2$SO$_4$	6-Chloro-3-propyl-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-propylacetoacetate	P$_2$O$_5$	6-Chloro-2-methyl-3-propyl-1,4,α,β-naphthapyrone	—	61
	Ethyl α-isobutylacetoacetate	H$_2$SO$_4$	6-Chloro-3-isobutyl-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-isobutylacetoacetate	P$_2$O$_5$	6-Chloro-2-methyl-3-isobutyl-1,4,α,β-naphthapyrone	—	61
	Ethyl α-phenylacetoacetate	H$_2$SO$_4$	6-Chloro-3-phenyl-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-benzylacetoacetate	H$_2$SO$_4$	6-Chloro-3-benzyl-4-methyl-1,2,α,β-naphthapyrone	—	61
	Diethyl acetosuccinate	H$_2$SO$_4$	Ethyl 6-chloro-4-methyl-1,2,α,β-naphthapyrone-3-acetate	—	61
	Diethyl acetosuccinate	H$_2$SO$_4$	Ethyl 6-chloro-4-methyl-1,2,α,β-naphthapyrone-3-acetate	—	42
			6-Chloro-4-methyl-1,2,α,β-naphthapyrone-3-acetic acid	—	
	Diethyl acetosuccinate	H$_2$SO$_4$ (80%)	6-Chloro-4-methyl-1,2,α,β-naphthapyrone-3-acetic acid	—	42
	Acetonedicarboxylic acid	H$_2$SO$_4$	6-Chloro-1,2,α,β-naphthapyrone-4-acetic acid	—	61
	Ethyl benzoylacetate	H$_2$SO$_4$	6-Chloro-4-phenyl-1,2,α,β-naphthapyrone	—	61
4-Bromo-α-naphthol	Ethyl acetoacetate	H$_2$SO$_4$; P$_2$O$_5$	6-Bromo-4-methyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-methylacetoacetate	H$_2$SO$_4$	6-Bromo-3,4-dimethyl-1,2,α,β-naphthapyrone	—	61
	Ethyl α-methylacetoacetate	P$_2$O$_5$	6-Bromo-2,3-dimethyl-1,4,α,β-naphthapyrone	—	61
	Ethyl α-benzylacetoacetate	H$_2$SO$_4$	6-Bromo-3-benzyl-4-methyl-1,2,α,β-naphthapyrone	—	61
4-Acetyl-α-naphthol	Ethyl acetoacetate	H$_2$SO$_4$; POCl$_3$	4-Methyl-1,2,α-naphthapyrone ‡	—	12
	Ethyl acetoacetate	AlCl$_3$	4-Methyl-1,2,α-naphthapyrone ‡	—	117
4-Propionyl-α-naphthol	Ethyl acetoacetate	H$_2$SO$_4$; POCl$_3$	4-Methyl-1,2,α-naphthapyrone §	—	12
	Ethyl acetoacetate	AlCl$_3$	4-Methyl-1,2,α-naphthapyrone §	—	117
4-Butyryl-α-naphthol	Ethyl acetoacetate	POCl$_3$	4-Methyl-1,2,α-naphthapyrone ‖	—	12

Note: References 142–244 are listed on pp. 57–58.

‡ An acetyl group was eliminated in the condensation.

§ A propionyl group was eliminated in the condensation.

‖ A butyryl group was eliminated in the condensation.

TABLE IV—*Continued*

CONDENSATIONS WITH NAPHTHOLS

Phenol	Acid or Ester	Condensing Agent	Product	Yield %	Reference
β-Naphthol	Malic acid	H_2SO_4	β-Naphthacoumarin	Poor	39
	Ethyl acetoacetate	H_2SO_4	4-Methyl-1,2,β,α-naphthapyrone	20–39	234, 23
	Ethyl acetoacetate	H_2SO_4	4-Methyl-1,2,β,α-naphthapyrone	25	110
			2-Methyl-1,4,β,α-naphthapyrone (isolated as styryl derivative)	Traces	
	Ethyl acetoacetate	H_2SO_4 (80%)	4-Methyl-1,2,β,α-naphthapyrone	70	155
	Ethyl acetoacetate	P_2O_5	2-Methyl-1,4,β,α-naphthapyrone	10	110
	Ethyl acetoacetate	CH_3CO_2Na	4-Methyl-1,2,β,α-naphthapyrone	—	127
			2-Methyl-1,4,β,α-naphthapyrone	—	
	Ethyl α-methylacetoacetate	H_2SO_4	3,4-Dimethyl-1,2,β,α-naphtha-pyrone	—	71
	Ethyl α-methylacetoacetate	P_2O_5	2,3-Dimethyl-1,4,β,α-naphtha-pyrone	—	71
	Ethyl α-ethylacetoacetate	P_2O_5	2-Methyl-3-ethyl-1,4,β,α-naphtha-pyrone	—	71
	Ethyl α-propylacetoacetate	P_2O_5	2-Methyl-3-propyl-1,4,β,α-naph-thapyrone	—	71
	Ethyl α-isopropylaceto-acetate	P_2O_5	2-Methyl-3-isopropyl-1,4,β,α-naphthapyrone	—	71
	Diethyl formylsuccinate	H_2SO_4	β-Naphthapyrone-3-acetic acid	—	76
	Diethyl acetosuccinate	H_2SO_4	4-Methyl-β-naphthapyrone-3-acetic acid	40	34, 76
	Ethyl γ-bromoacetoacetate	H_2SO_4	4-Bromomethyl-β-naphthapyrone	—	83
	Acetonedicarboxylic acid	H_2SO_4	4,3,β-naphthapyrone-1-acetic acid	—	26
	Diethyl oxalacetate	H_2SO_4	Ethyl 4,3,β-naphthapyrone-carboxylate	—	26
	Ethyl benzoylacetate	P_2O_5	β-Naphthoflavone	30	236
	Ethyl cyclopentanone-2-carboxylate	P_2O_5	Cyclopenteno-(1',2',2,3)-1,4-β,α-naphthapyrone	—	11
1,5-Dihydroxy-naphthalene	Ethyl acetoacetate	HCl	6'-Hydroxy-4-methyl-7,8-benzo-coumarin	92	237
	Ethyl acetoacetate	$AlCl_3$	6'-Hydroxy-4-methyl-7,8-benzo-coumarin	78	237
	Diethyl α-acetylglutarate	H_2SO_4	Diethyl 4,4'-dimethylnaphtha-dipyrone-3,3'-dipropionate	—	238

Note: References 142–244 are listed on pp. 57–58.

TABLE V

CONDENSATIONS WITH MISCELLANEOUS COMPOUNDS

Compound	Acid or Ester	Condensing Agent	Product	Yield %	Reference
1,2,3-Trihydroxy-4-methoxybenzene	Malic acid	H_2SO_4	6,7,8-Trihydroxycoumarin *		239
Lecanoric acid	Malic acid	H_2SO_4	5-Hydroxy-7-methylcoumarin		242
Thiophenol	Methyl α-methylaceto-acetate	P_2O_5	2,3-Dimethyl-1-thiochromone	17	243
Thiotolenol	Ethyl acetoacetate	H_2SO_4	4,6-Dimethylthiophenol-1,2-pyrone	—	42

Note: References 142–244 are listed on pp. 57–58.
* Demethylation took place during the reaction.

TABLE V—*Continued*

Condensations with Miscellaneous Compounds

Compound	Acid or Ester	Condensing Agent	Product	Yield %	Reference
Ethyl 2-methyl-4-hydroxythiophene-3-carboxylate	Ethyl acetoacetate	H_2SO_4	Ethyl 4,6-dimethyl-5-thiocoumarin-7-carboxylate	31	65
	Ethyl α-methylacetoacetate	H_2SO_4	Ethyl 3,4,6-trimethyl-5-thiocoumarin-7-carboxylate	—	65
	Diethyl acetylsuccinate	H_2SO_4	Ethyl 4,6-dimethyl-5-thio-7-carbethoxycoumarin-3-acetate	—	65
	Acetonedicarboxylic acid	H_2SO_4	6-Methyl-7-carbethoxy-5-thiocoumarin-4-acetic acid	17	65
	Ethyl o-cyclohexanone-carboxylate	H_2SO_4	Ethyl 3,4-cyclohexenyl-6-methyl-5-thiocoumarin-7-carboxylate	46	65
7-Hydroxycoumarin	Malic acid	H_2SO_4	Coumaro-7,6(or 7,8)-α-pyrone	60	63
	Malic acid	H_2SO_4	Coumarino-7,8,α-pyrone	53	62
			Coumarino-7,6,α-pyrone	3	
7-Hydroxy-4-methylcoumarin	Malic acid	H_2SO_4	4-Methylcoumarino-7,8,α-pyrone	—	62
	Malic acid	H_2SO_4	4-Methylcoumaro-7,6(or 7,8)-α-pyrone	70	63
	Ethyl acetoacetate	H_2SO_4	4,4'-Dimethylcoumaro-7,6(or 7,8)-α-pyrone	30	63
	Ethyl acetoacetate	H_2SO_4	4,4'-Dimethylcoumarino-7,8,α-pyrone	15	62
7-Hydroxy-3-chloro-4-methylcoumarin	Malic acid	H_2SO_4	3-Chloro-4-methylcoumaro-7,6(7,8)-α-pyrone	30	241
5-Hydroxy-7-methylcoumarin	Malic acid	H_2SO_4	7-Methylcoumaro-5,6,α-pyrone	50	63
5-Hydroxy-4,7-dimethylcoumarin	Malic acid	H_2SO_4	4,7-Dimethylcoumaro-5,6,α-pyrone	65	63
	Ethyl acetoacetate	H_2SO_4	4,4',7-Trimethylcoumaro-5,6,α-pyrone	15	63
5-Hydroxy-3-chloro-4,7-dimethylcoumarin	Malic acid	H_2SO_4	3-Chloro-4,7-dimethylcoumaro-5,6,α-pyrone	20	241
7,8-Dihydroxycoumarin	Malic acid	H_2SO_4	8-Hydroxycoumaro-7,6,α-pyrone	40	63
7,8-Dihydroxy-4-methylcoumarin	Malic acid	H_2SO_4	8-Hydroxy-4-methylcoumaro-7,6,α-pyrone	55	63
7,8-Dihydroxy-3-chloro-4-methylcoumarin	Malic acid	H_2SO_4	8-Hydroxy-3-chloro-4-methylcoumaro-7,6,α-pyrone	—	241
5,7-Dihydroxy-4-methylcoumarin	Malic acid	H_2SO_4	5-Hydroxy-4-methylcoumaro-7,8,α-pyrone or 7-hydroxy-4-methylcoumaro-5,6,α-pyrone	60	63
6'-Hydroxy-4-methyl-7,8-benzocoumarin	Ethyl acetoacetate	H_2SO_4 (85%)	4,4'-Dimethyl-7,8,8',7'-coumarino-coumarin	—	237
2,2-Dimethyl-7-hydroxychromanone	Malic acid	H_2SO_4	Dimethyldihydroxypyronocoumarin	—	242
7(?)-Hydroxy-2,4,4-trimethyl-3,4-dihydroquinoline	Ethyl acetoacetate	$ZnCl_2$	4,6,6,8-Tetramethyl-6,7-dihydroquinocoumarin	—	121
6-Hydroxycoumaran	Malic acid	H_2SO_4	4',5'-Dihydro-2',3',7,6-furocoumarin (4',5-dihydropseoralen)	51	243
6,7-Dihydroxycoumaran	Malic acid	H_2SO_4	4',5'-Dihydro-8-hydroxy-2',3',7,6-furocoumarin (4',5'-dihydroxanthotoxol)	30	244

REFERENCES TO TABLES I–V

[142] Simonis and Goldenzweig, *Ber.*, **48**, 1583 (1915).

[143] Mentzer and Meunier, *Bull. soc. chim. France*, **11**, 302 (1944) [*C. A.*, **40**, 1832 (1946)].

[144] Peters and Simonis, *Ber.*, **41**, 830 (1908).

[145] Limaye, *J. Indian Chem. Soc.*, **4**, 159 (1927).

[146] Plant, *J. Chem. Soc.*, **1933**, 1586.

[147] Pechmann and Schwarz, *Ber.*, **32**, 3696 (1899).

[148] de Benneville and Connor, *J. Am. Chem. Soc.*, **62**, 3067 (1940).

[149] Fries and Volk, *Ann.*, **379**, 90 (1911).

[150] Dey and Radhabai, *J. Indian Chem. Soc.*, **11**, 635 (1934).

[151] Müller, *Ber.*, **58**, 2202 (1925).

[152] Meunier, Mentzer, and Vinet, *Helv. Chim. Acta*, **29**, 1291 (1946).

[153] Buluigina, *Masloboina Zhirovoe Delo*, **1934**, No. 4, 43 [*C. A.*, **30**, 1776 (1936)].

[154] Hantzsch and Lang, *Ber.*, **19**, 1298 (1886).

[155] Patel and Bokil, *J. Univ. Bombay*, **11**, (pt. 3), 92 (1943) [*C. A.*, **37**, 5969 (1943)].

[156] Auwers and Meissner, *Ann.*, **439**, 132 (1924).

[157] Alles, Icke, and Feigen, *J. Am. Chem. Soc.*, **64**, 2031 (1942).

[158] McPhee and Ball, *J. Am. Chem. Soc.*, **66**, 1636 (1944).

[159] Dey and Dalal, *J. Chem. Soc.*, **123**, 3384 (1923).

[160] Simonis, *Ber.*, **50**, 779 (1917).

[161] Flynn and Robertson, *J. Chem. Soc.*, **1936**, 215.

[162] Adams and Mecorney, *J. Am. Chem. Soc.*, **67**, 798 (1945).

[163] Simonis and Hervoici, *Ber.*, **50**, 787 (1917).

[164] Mitsui, Sudzuki, and Yoshinaga, *J. Chem. Soc. Japan*, **64**, 1337 (1943) [*C. A.*, **41**, 4488 (1947)].

[165] Werder, Moll, and Jung, *Z. physiol. Chem.*, **257**, 129 (1939) [*C. A.*, **33**, 3398 (1939)].

[166] Heilbron, Barnes, and Morton, *J. Chem. Soc.*, **123**, 2559 (1923).

[167] Baker, *J. Chem. Soc.*, **1927**, 2898.

[168] Pavolino, *Atti Congr. naz. chim. pura applicata, 4th Congr. Rome and Abruzzo (1932)*, **1933**, 557 [*C. A.*, **29**, 4342 (1935)].

[169] Shamshurin, *Trudy Uzbek. Gosudarst. Univ. Sbornik Rabot Khim.*, **15**, 33 (1939) [*C. A.*, **35**, 3994 (1941)].

[170] Hantzsch and Zürcher, *Ber.*, **20**, 1328 (1887).

[171] Mentzer, Gley, Molho, and Billet, *Bull. soc. chim. France*, **1946**, 271 [*C. A.*, **40**, 6066 (1946)].

[172] Naik, Desai, and Trivedi, *J. Indian Chem. Soc.*, **6**, 801 (1929).

[173] Shah, *J. Univ. Bombay*, **8** (pt. 3), 205 (1939) [*C. A.*, **34**, 2821 (1940)].

[174] Bülow, *Ber.*, **36**, 190 (1903).

[175] Borsche and Lewinsohn, *Ber.*, **66**, 1792 (1933).

[176] Bogert and Isham, *J. Am. Chem. Soc.*, **36**, 514 (1914).

[177] Fries and Lindemann, *Ann.*, **404**, 53 (1914).

[178] Seshadri and Venkateswarlu, *Proc. Indian Acad. Sci.*, **14A**, 297 (1941) [*C. A.*, **36**, 2536 (1942)].

[179] Balaiah, Seshadri, and Venkateswarlu, *Proc. Indian Acad. Sci.*, **16A**, 68 (1942) [*C. A.*, **37**, 1429 (1943)].

[180] Yanagita, *Ber.*, **71**, 2269 (1938).

[181] Shah and Shah, *J. Indian Chem. Soc.*, **19**, 489 (1942).

[182] Adams, Cain, and Loewe, *J. Am. Chem. Soc.*, **63**, 1977 (1941).

[183] Limaye and Ghate, *Rasayanam*, **1**, 169 (1939) [*C. A.*, **34**, 5072 (1940)].

[184] Limaye and Limaye, *Rasayanam*, **1**, 201 (1941) [*C. A.*, **36**, 1038 (1942)].

[185] Chakravarti and Chakravarty, *J. Indian Chem. Soc.*, **16**, 144 (1939).

[186] Desai and Ekhlas, *Proc. Indian Acad. Sci.*, **8A**, 194 (1938) [*C. A.*, **33**, 2119 (1939)].

[187] Thakor and Shah, *J. Univ. Bombay*, **15** (pt. 5), 14 (1947) [*C. A.*, **42**, 1244 (1948)].

[188] Chudgar and Shah, *J. Univ. Bombay*, **11** (pt. 3), 116 (1942) [*C. A.*, **37**, 2002 (1943)].

[189] Haller and Acree, *J. Am. Chem. Soc.*, **56**, 1389 (1934).

[190] Spath, Takei, and Miyajima, *Ber.*, **67**, 262 (1934).

[121] Takei, Miyajima, and Ōno, *Sci. Papers Inst. Phys. Chem. Research Tokyo*, **24**, 1 (1934) [*C. A.*, **28**, 4730 (1934)].

[122] Yamashita, *Bull. Chem. Soc. Japan*, **8**, 276 (1933) [*C. A.*, **28**, 135 (1934)].

[123] Adams, U. S. pat., 2,354,492 (1944) [*C. A.*, **39**, 3126 (1945)].

[124] Adams and Baker, *J. Am. Chem. Soc.*, **62**, 2401 (1940).

[125] Twiss, *J. Am. Chem. Soc.*, **48**, 2206 (1926).

[126] Chudgar and Shah, *J. Univ. Bombay*, **11** (pt. 3), 113 (1942) [*C. A.*, **37**, 2002 (1943)].

[127] Adams, Chen, and Loewe, *J. Am. Chem. Soc.*, **67**, 1534 (1945).

[128] Adams, Aycock, and Loewe, *J. Am. Chem. Soc.*, **70**, 662 (1948).

[129] Adams, Mackenzie, and Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948).

[200] Arima, *Bull. Chem. Soc. Japan*, **4**, 113 (1929) [*C. A.*, **23**, 4708 (1929)].

[201] Bruchhausen and Hoffmann, *Ber.*, **74**, 1584 (1941).

[202] Gaind, Gupta, and Ray, *Curr. Sci.*, **5**, 646 (1937) [*C. A.*, **31**, 7415 (1937)].

[203] Desai and Hamid, *Proc. Indian Acad. Sci.*, **6A**, 185 (1937) [*C. A.*, **32**, 1254 (1938)].

[204] Limaye and Shenolikar, *Rasayanam*, **1**, 93 (1937) [*C. A.*, **32**, 2096 (1938)].

[205] Limaye and Talwalkar, *Rasayanam*, **1**, 141 (1938) [*C. A.*, **33**, 1698 (1939)].

[206] Clayton, *J. Chem. Soc.*, **97**, 1388 (1910).

[207] Desai and Mavani, *Proc. Indian Acad. Sci.*, **25A**, 341, 353 (1947) [*C. A.*, **42**, 1913–14 (1948)].

[208] Limaye and Mavani, *Rasayanam*, **1**, 109 (1937) [*C. A.*, **32**, 2095 (1938)].

[209] Shah and Mehta, *J. Indian Chem. Soc.*, **13**, 358 (1936).

[210] Shah and Mehta, *J. Univ. Bombay*, **4** (pt. 2), 109 (1935) [*C. A.*, **30**, 5196 (1936)].

[211] Sethna and Shah, *J. Chem. Soc.*, **1938**, 1066.

[212] Sethna and Shah, *J. Indian Chem. Soc.*, **17**, 211 (1940).

[213] Sastry and Seshadri, *Proc. Indian Acad. Sci.*, **12A**, 498 (1940) [*C. A.*, **35**, 3626 (1941)].

[214] Desai and Vakil, *Proc. Indian Acad. Sci.*, **12A**, 357 (1940) [*C. A.*, **35**, 3639 (1941)].

[215] Desai and Gaitonde, *Proc. Indian Acad. Sci.*, **25A**, 364 (1947) [*C. A.*, **42**, 1915 (1948)].

[216] Thakor and Shah, *J. Indian Chem. Soc.*, **23**, 423 (1946).

[217] Borsche, *Ber.*, **40**, 2731 (1907).

[218] Heilbron and Howard, *J. Chem. Soc.*, **1934**, 1571.

[219] Desai and Mavani, *Proc. Indian Acad. Sci.*, **25A**, 327 (1947) [*C. A.*, **42**, 541 (1948)].

[220] Werder and Jung, *Ber.*, **71**, 2638 (1938).

[221] John, Günther, and Schmeil, *Ber.*, **71**, 2637 (1938).

[222] Kostanecki and Weber, *Ber.*, **26**, 2906 (1895).

[223] Bargellini and Grippa, *Gazz. chim. ital.*, **57**, 138 (1927) [*C. A.*, **21**, 1981 (1927)].

[224] Yamashita, *Science Repts. Tôhoku Imp. Univ.*, First Ser., **24**, 202 (1935) [*C. A.*, **29**, 7327 (1935)].

[225] Pechmann and Kraft, *Ber.*, **34**, 423 (1901).

[226] Baker and Evans, *J. Chem. Soc.*, **1938**, 372.

[227] Amiard and Allais, *Bull. soc. chim. France*, **1947**, 512 [*C. A.*, **42**, 541 (1948)].

[228] Badhwar and Venkataraman, *J. Chem. Soc.*, **1932**, 2420.

[229] Pechmann and Cohen, *Ber.*, **17**, 2187 (1884).

[230] Schmid, *Helv. Chim. Acta*, **30**, 1661 (1947).

[231] King and Robertson, *J. Chem. Soc.*, **1934**, 403.

[232] Späth, Dey, and Tyray, *Ber.*, **72**, 53 (1939).

[233] Bartsch, *Ber.*, **36**, 1966 (1903).

[234] Bacovescu, *Ber.*, **43**, 1280 (1910).

[235] Murty, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, **6A**, 317 (1937) [*C. A.*, **32**, 3362 (1938)].

[236] Schönberg, Rosenbach, Krüll, and Ostwald, *Ber.*, **58**, 1793 (1925).

[237] Robinson and Weygand, *J. Chem. Soc.*, **1941**, 386.

[238] Shamshurin, *J. Gen. Chem. U.S.S.R.*, **14**, 885 (1944) [*C. A.*, **39**, 3789 (1945)].

[239] Späth and Dobrovolny, *Ber.*, **71**, 1831 (1938).

[240] Simonis and Elias, *Ber.*, **49**, 768 (1916).

[241] Biswas, *Science and Culture*, **2**, 225 (1936) [*C. A.*, **31**, 4317 (1937)].

[242] Arima, *J. Chem. Soc. Japan*, **53**, 715 (1932) [*C. A.*, **27**, 295 (1933)].

[243] Späth, Manjunath, Pailer, and Jois, *Ber.*, **69**, 1086 (1936).

[244] Späth and Pailer, *Ber.*, **69**, 767 (1936).

CHAPTER 2

THE SKRAUP SYNTHESIS OF QUINOLINES

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CONTENTS

INTRODUCTION

Koenigs[1] first synthesized quinoline in 1879 by passing allylaniline over heated litharge. Shortly thereafter[2] he prepared quinoline by heating the condensation product of aniline and acrolein, thus antici-

[1] Koenigs, *Ber.*, **12**, 453 (1879).
[2] Koenigs, *Ber.*, **13**, 911 (1880).

pating the classical Skraup synthesis. This synthesis involves a series of reactions brought about by heating a primary aromatic amine, in which at least one position *ortho* to the amino group is unsubstituted, with glycerol, sulfuric acid, and an oxidizing agent. The product is a quinoline containing only those substituents that were originally present in the aromatic amine. Quinolines substituted in the hetero ring may be obtained by a modified Skraup synthesis in which a substituted acrolein or a vinyl ketone is used in place of glycerol.

MECHANISM

The Skraup reaction takes place through four successive steps: dehydration of glycerol to acrolein under the influence of sulfuric acid; addition of the aromatic amine to acrolein to form an intermediate β-arylaminoaldehyde (III); ring closure by dehydration to form 1,2-di-hydroquinoline (IV); and oxidation of IV to quinoline (V). The re-

placement of glycerol by acrolein in the reaction with aniline, sulfuric acid, and an oxidizing agent under ordinary conditions results in much resinification and only a little quinoline.[3] However, a high yield of quinoline can be obtained by passing acrolein vapor into the solution of aniline, sulfuric acid, and an oxidizing agent under proper conditions.[4, 5] The nitroanilines and the nitromethoxyanilines react readily with liquid acrolein to give good yields of the corresponding substituted quinolines,[6, 7, 8] especially when sulfuric acid is replaced by phosphoric acid.[7]
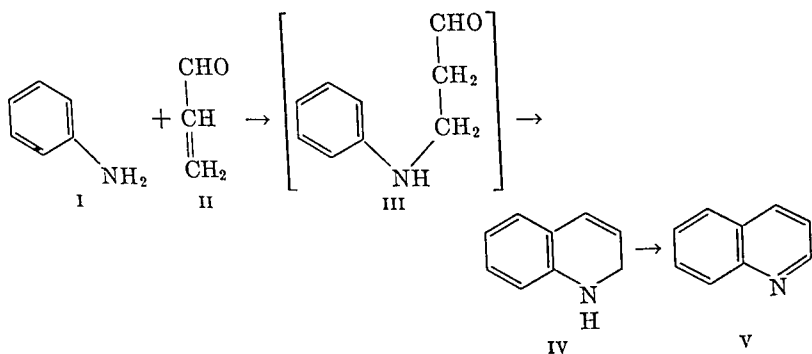
[3] Manske, unpublished observations.
[4] Tchitchibabin, Swiss pat. 240,991 (1946).
[5] Kulka, unpublished observations.
[6] Yale, *J. Am. Chem. Soc.*, **69**, 1230 (1947).
[7] Yale and Bernstein, *J. Am. Chem. Soc.*, **70**, 254 (194
[8] Yale, *J. Am. Chem. Soc.*, **70**, 1982 (1948).

Skraup had suggested originally that the aromatic amine condensed with acrolein to form a Schiff base (VI), but this cannot be correct. If it were, β-methylacrolein (crotonaldehyde) should yield as an intermediate the Schiff base VII, which on ring closure would give 4-methyl-

quinoline (lepidine).   The product, however, is 2-methylquinoline (quinaldine), and therefore the intermediate must be the β-arylamino-aldehyde VIII or a Schiff base derived from it.[9]
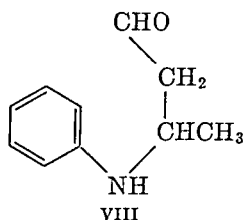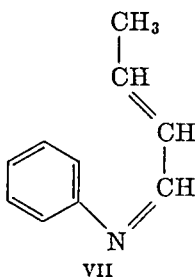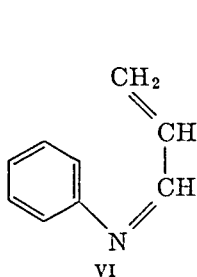
SCOPE AND LIMITATIONS

The Skraup reaction is of great general utility and has been applied to many aromatic amines.   The only amines that fail to give the desired quinolines are those having substituents too reactive to withstand the drastic conditions, e.g., labile substituents such as acetyl, cyano, methoxyl, and fluoro.   p-Aminoacetophenone,[10] 2-cyano-5-methylaniline,[11] p-methoxyaniline,[12] 3-nitro-4,5-dimethoxyaniline,[13] 2-nitro-4-methoxy-5-fluoroaniline,[13] and 3-nitro-4-aminoveratrole[14] fail to give the corresponding quinoline derivatives because the substituents are either degraded or hydrolyzed by the hot, strong sulfuric acid used in the reaction.   The hydrolytic action of the sulfuric acid can be minimized by reducing the reaction time from the usual several hours to a few minutes.[13]   With a reaction time of one and one-half minutes 8-nitro-5,6-dimethoxyquinoline was prepared from 2-nitro-4,5-dimethoxyaniline in 40% yield.[13]

The original Skraup synthesis has been extended to include the preparation of quinolines substituted in the pyridine ring through the

[9] Manske, *Chem. Revs.*, **30**, 113 (1942).

[10] Berend and Thomas, *Ber.*, **25**, 2548 (1892).

[11] v. Jakubowski, *Ber.*, **43**, 3026 (1910).

[12] Kaslow and Raymond, *J. Am. Chem. Soc.*, **68**, 1102 (1946).

[13] Elderfield, Gensler, Williamson, Griffing, Kupchan, Maynard, Kreysa, and Wright, *J. Am. Chem. Soc.*, **68**, 1584 (1946).

[14] Frisch, Silverman, and Bogert, *J. Am. Chem. Soc.*, **65**, 2432 (1943).

use of α,β-unsaturated aldehydes and ketones. 2-Methylquinolines (X) are obtained in high yield by adding β-methylacrolein (crotonaldehyde) (IX),[15] its diacetate,[15] or 1,1,3-trimethoxybutane [16] to a stirred mixture
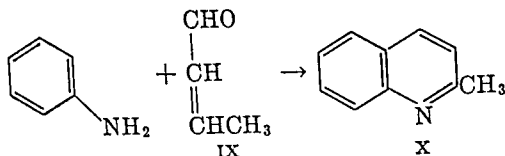
of sulfuric acid, an oxidant, and an aromatic amine at such a rate that violent reaction is avoided. 2-Arylquinolines are prepared similarly by employing β-phenylacrolein (cinnamaldehyde) in place of croton-aldehyde.[17,18,19] The use of an α-substituted acrolein (XI) [8,15,20] or a 2-substituted glycerol [21,22,23] as an addend in the Skraup reaction results in a quinoline substituted in the 3 position (XII, R = methyl, aryl, or halogen). The acetal, the diacetate, or the dipropionate of the α-substituted acrolein is often preferred in order to avoid the polymeri-

zation of part of the aldehyde during the reaction.[15,20]
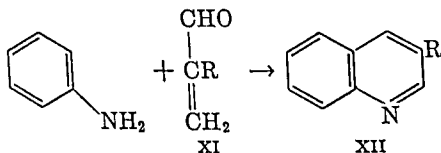
While engaged in a study of antimalarial compounds, Campbell and co-workers [16,24-27] synthesized some 4-methylquinolines (XIV, R = methyl) by condensing methyl vinyl ketone (XIII, R = methyl) with aromatic amines under conditions somewhat milder than those used by Skraup. In view of the fact that α,β-unsaturated ketones such as XIII polymerize to some extent under the conditions of the reaction, it has

[15] Utermohlen, *J. Org. Chem.*, **8**, 544 (1943).

[16] Campbell, Helbing, and Kerwin, *J. Am. Chem. Soc.*, **68**, 1840 (1946).

[17] Murmann, *Monatsh.*, **25**, 621 (1904).

[18] Grimaux, *Compt. rend.*, **96**, 584 (1883).

[19] Elderfield, Gensler, Bembry, Williamson, and Weisl, *J. Am. Chem. Soc.*, **68**, 1589 (1946).

[20] Manske, Marion, and Leger, *Can. J. Research*, **20B**, 133 (1942).

[21] Darzens and Meyer, *Compt. rend.*, **198**, 1428 (1934).

[22] Warren, *J. Chem. Soc.*, **1936**, 1366.

[23] Brown and Dougherty, *J. Am. Chem. Soc.*, **69**, 2232 (1947).

[24] Campbell and Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945).

[25] Campbell, Sommers, Kerwin, and Campbell, *J. Am. Chem. Soc.*, **68**, 1851 (1946).

[26] Campbell, Sommers, Kerwin, and Campbell, *J. Am. Chem. Soc.*, **68**, 1556 (1946).

[27] Campbell, Elderfield, Gensler, Sommers, Kremer, Kupchan, Tinker, Dressner, Romanek, and Campbell, *J. Am. Chem. Soc.*, **69**, 1465 (1947).

been found expedient to employ compounds that will yield the α,β-unsaturated ketones under these conditions. Thus β-ketobutanol,[20, 28, 29]

XIII   XIV
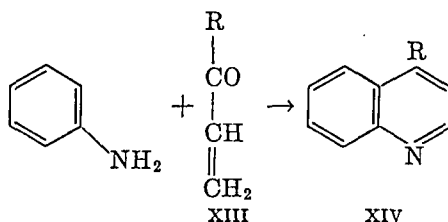
methyl β-chloroethyl ketone,[30, 31, 32] 4-methoxy-2-butanone,[24] and 1,3,3-trimethoxybutane [24-27, 33] when condensed with aniline all yield 4-methylquinoline, presumably via methyl vinyl ketone. 1-Aryl-3-chloropropan-1-ones are used for the preparation of 4-arylquinolines (XIV, R = phenyl).[30, 34]

Aroquinolines

Amino derivatives of such fused systems as naphthalene, anthracene, phenanthrene, and pyrene undergo the Skraup reaction readily, and the resulting products are classed as aroquinolines. With 1-naphthylamine only one compound, benzo(h)quinoline (XV), is possible,[22, 35-41] but 2-naphthylamine might react with glycerol in two ways to produce a mixture of the two isomers, benzo(f)quinoline (XVI) and benzo(g)quinoline (XVII). The ring closure actually takes place in the 1 position of 2-naphthylamine, and benzo(f)quinoline (XVI) is the only product.[36, 42-48]

[28] Prill and Walter, Ger. pat. 505,320 [*C. A.*, **26**, 479 (1932)].

[29] I. G. Farbenindustrie A.G., Brit. pat. 308,365 [*C. A.*, **24**, 128 (1930)].

[30] Kenner and Statham, *Ber.*, **69**, 16 (1936).

[31] Schering-Kahlbaum A.G., Brit. pat. 283,577 [*C. A.*, **22**, 4132 (1928)].

[32] Zöllner, U. S. pat. 1,804,045 [*C. A.*, **25**, 3668 (1931)].

[33] Campbell and Kerwin, *J. Am. Chem. Soc.*, **68**, 1837 (1946).

[34] Kenner and Statham, *J. Chem. Soc.*, **1935**, 299.

[35] Skraup, *Ber.*, **14**, 1002 (1881).

[36] Skraup, *Ber.*, **15**, 893 (1882); *Monatsh.*, **3**, 531 (1882).

[37] Farbwerke vorm Meister, Lucius, and Brüning, Ger. pat. 26,430 (1883) [*Frdl.*, **1**, 183 (1877–1887)].

[38] I. G. Farbenindustrie A.G., Fr. pat. 727,528 [*C. A.*, **26**, 5104 (1932)].

[39] Claus and Imhoff, *J. prakt. Chem.*, [2] **57**, 68 (1898).

[40] Bamberger and Stettenheimer, *Ber.*, **24**, 2472 (1891).

[41] Schenkel and Schenkel, *Helv. Chim. Acta*, **27**, 1456 (1944).

[42] Mikhailov, *Novosti Tekhniki*, **1940**, No. 3–4, 51 [*C. A.*, **34**, 5847 (1940)].

[43] Knueppel, *Ber.*, **29**, 703 (1896).

[44] Claus and Besseler, *J. prakt. Chem.*, [2] **57**, 49 (1898).

[45] Bamberger and Müller, *Ber.*, **24**, 2641 (1891).

[46] Clem and Hamilton, *J. Am. Chem. Soc.*, **62**, 2349 (1940).

[47] Sergeev, *Byull. Lako-Krasochnoi Prom.*, **1938**, No. 2–3, 68; *Khim. Referat. Zhur.*, **2**, No. 1, 102 [*C. A.*, **34**, 1665 (1940)].

[48] Skraup and Cobenzl, *Monatsh.*, **4**, 436 (1883).
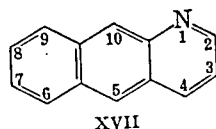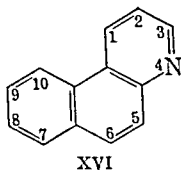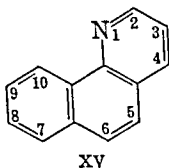
So strong is the tendency for ring closure to occur in the 1 position that a substituent such as halogen or nitro (but not methyl) in that position in 2-naphthylamine is eliminated. Thus 1-nitro-,[49, 50] 1-bromo-,[49, 50] and 1-chloro-2-naphthylamine [51, 52] when subjected to the Skraup reaction yield benzo(ƒ)quinoline (XVI) alone or in admixture with the corresponding 10-substituted benzo(g)quinoline. In contrast to this, 5,6,7,8-tetrahydro-2-naphthylamine undergoes the Skraup reaction to yield a mixture of 7,8,9,10-tetrahydrobenzo(ƒ)quinoline and 6,7,8,9-tetrahydrobenzo(g)quinoline, with the latter predominating.[53]   Other amines that undergo this reaction are 1-, 2-, 3-, 4-, and 9-aminophenanthrene,[54, 55, 56] 3-aminopyrene,[57] 3-aminoacenaphthene,[58] 1- and 2-aminoanthraquinone,[43, 59-64] and 2-aminofluorene.[65] Heterocyclic amines such as 3-aminopyridine,[66] 2-aminothiophene,[67] and the aminobenzopyrones [68, 69] do not withstand the drastic conditions well, and therefore the yields of the resulting quinoline derivatives in general are poor.

Aromatic diamines react with two moles of glycerol to give products known as phenanthrolines.   The preparation of 1,7- (XVIII) [36, 43, 70, 71, 72]

[49] Lellmann and Schmidt, *Ber.*, **20**, 3154 (1887).

[50] Huisgen, *Ann.*, **559**, 101 (1948).

[51] Gerhardt and Hamilton, *J. Am. Chem. Soc.*, **66**, 479 (1944).

[52] Clemo and Driver, *J. Chem. Soc.*, **1945**, 829.

[53] v. Braun and Gruber, *Ber.*, **55**, 1710 (1922).

[54] Herschmann, *Ber.*, **41**, 1998 (1908).

[55] Cook and Thomson, *J. Chem. Soc.*, **1945**, 395.

[56] Mosettig and Krueger, *J. Org. Chem.*, **3**, 317 (1938).

[57] Vollmann, Becker, Corell, Streeck, and Langbein, *Ann.*, **531**, 1 (1937).

[58] Zinke and Raith, *Monatsh.*, **40**, 271 (1919).

[59] Delaby and Hiron, *Bull. soc. chim. France*, [4] **47**, 227, 1395 (1930).

[60] Majert, Ger. pat. 26,197 [*Frdl.*, **1**, 171 (1877–1887)].

[61] Farbwerke vorm Meister, Lucius, and Brüning, Ger. pat. 189,234 [*Frdl.*, **8**, 1362 (1905–1907)].

[62] Badische Anilin- und Sodafabrik, Ger. pat. 171,939 [*Frdl.*, **8**, 369 (1905–1907)].

[63] Schaarschmidt and Stahlschmidt, *Ber.*, **45**, 3452 (1912).

[64] Graebe, *Ann.*, **201**, 333 (1880).

[65] Hughes, Lions, and Wright, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 449 (1938) [*C. A.*, **33**, 609 (1939)].

[66] Allen, *Chem. Revs.*, **47**, 275 (1950).

[67] Steinkopf and Lützkendorf, *Ann.*, **403**, 45 (1914).

[68] Dey and Goswami, *J. Chem. Soc.*, **115**, 531 (1919).

[69] Dhar, *J. Chem. Soc.*, **117**, 1053 (1920).

[70] Druce, *Chem. News*, **119**, 271 (1919) [*C. A.*, **14**, 535 (1920)].

[71] Smith, *J. Am. Chem. Soc.*, **52**, 397 (1930).

[72] Skraup and Vortmann, *Monatsh.*, **3**, 570 (1882); **4**, 569 (1883).

and 4,7-phenanthroline (XIX) [36, 70-74] from m- and p-phenylenediamine, respectively, offers no difficulties. Although some workers have reported failure of attempts to prepare 1,10-phenanthroline (XX) from o-phenylenediamine,[71, 75] others have reported yields of 30–45%.[76, 77] A
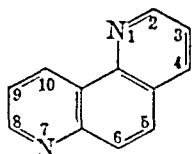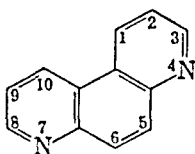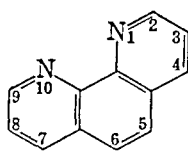
far better method for preparing 1,10-phenanthroline is to subject 8-aminoquinoline [71, 78] or its derivatives [79, 80] to the Skraup reaction. 8-Aminoquinolines are readily obtained from the corresponding o-nitroanilines by way of the 8-nitroquinolines. It is to be noted that 5- and 6-substituted 8-aminoquinolines yield identical phenanthroline derivatives. 4-Aminoquinolines [81, 82] and 5-aminoisoquinolines [75] undergo the Skraup reaction, but the yields are poor.

A double Skraup reaction also occurs with a diaminobiphenyl. A
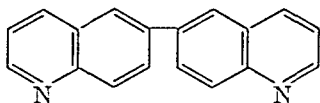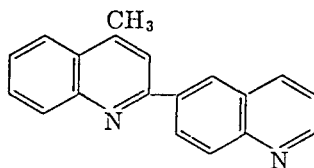
good example is the preparation of 6,6'-biquinolyl (XXI) from 4,4'-diaminobiphenyl (benzidine).[83, 84, 85] Another method for the preparation of biquinolyls is the Skraup synthesis with an anilinoquinoline, e.g., 4-methyl-2,6'-biquinolyl (XXII) from 2-p-anilino-4-methylquinoline.[86]

[73] Haskelberg, *J. Am. Chem. Soc.*, **69**, 1538 (1947).

[74] Douglas, Jacomb, and Kermack, *J. Chem. Soc.*, **1947**, 1659.

[75] Misani and Bogert, *J. Org. Chem.*, **10**, 347 (1945).

[76] Halcrow and Kermack, *J. Chem. Soc.*, **1946**, 155.

[77] Breckenridge and Singer, *Can. J. Research*, **25B**, 583 (1947).

[78] Smith and Getz, *Chem. Revs.*, **16**, 113 (1935).

[79] Richter and Smith, *J. Am. Chem. Soc.*, **66**, 396 (1944).

[80] Burger, Bass, and Fredericksen, *J. Org. Chem.*, **9**, 373 (1944).

[81] Marckwald, *Ann.*, **279**, 20 (1894).

[82] Lions and Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 443 (1941) [*C. A.*, **35**, 4771 (1941)].

[83] Roser, *Ber.*, **17**, 1817, 2767 (1884).

[84] Ostermayer and Henrichsen, *Ber.*, **17**, 2444 (1884).

[85] Fischer, *Monatsh.*, **5**, 417 (1884).

[86] Fischer, *Ber.*, **19**, 1036 (1886).

5-Aminohydrindene also follows this rule, yielding a mixture of 6,7-trimethylene- and 5,6-trimethylene-quinoline in the ratio of 9:1.[94]

Application of the Skraup synthesis to 2-naphthylamine,[36, 42–48] 2-aminofluorene,[65] and 2-aminophenanthrene[56] yields the angular isomers only, benzo(*f*)quinoline (XVI), 11-indeno(*2,1-f*)quinoline (XXIII), and naphtho(*2,1-f*)quinoline (XXIV), respectively. On the
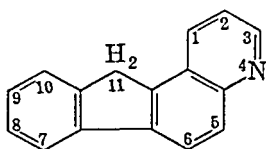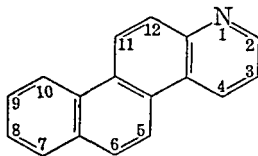
XXIII   XXIV

other hand, 5,6,7,8-tetrahydro-2-naphthylamine[53] gives a mixture in which the linear isomer, 6,7,8,9-tetrahydrobenzo(*g*)quinoline, predominates. Like 2-naphthylamine, 6-aminoquinoline undergoes the Skraup ring closure in the 5 position to yield the angular isomer, 4,7-phenanthroline (XIX), exclusively. 5-Nitro- and 5-bromo-6-amino-quinoline also lose the 5 substituent on cyclization to form 4,7-phenanthroline. 5-Methyl-6-aminoquinoline retains its 5 substituent, and the product is 10-methyl-1,6-anthrazoline (XXV).[50] 7-Aminoquinoline undergoes the Skraup reaction to yield the angular isomer, 1,7-phenan-
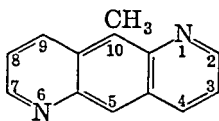
XXV   XXVI
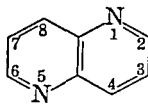
throline (XVIII), only. With 3-aminopyridine and 3-amino-2-chloro-pyridine the cyclization takes place at the 2 position to form only the linear compound, XXVI (1,5-naphthyridine), the halogen being eliminated in the latter case. The cyclization at the 4 position is evidently difficult since 3-amino-2,6-dimethylpyridine will not undergo the Skraup reaction.[66] 3-Aminodibenzofuran produces a mixture of the two isomeric quinolines.[95, 96, 97]

Determination of the Identities of 5- and 7-Substituted Quinolines

In determining the identity of the two isomeric quinolines formed from *meta*-substituted anilines in the Skraup reaction, the synthesis of

[94] Lindner, Sellner, Hofmann, and Hager, *Monatsh.*, **72**, 335, 354 (1939).

[95] Mosettig and Robinson, *J. Am. Chem. Soc.*, **57**, 902 (1935).

[96] Kirkpatrick and Parker, *J. Am. Chem. Soc.*, **57**, 1123 (1935).

[97] Adams, Clark, Kornblum, and Wolff, *J. Am. Chem. Soc.*, **66**, 22 (1944).

one or both isomers by unambiguous methods is necessary. The most common method is to block one of the *ortho* positions of the *meta*-substituted aniline, subject it to the Skraup reaction, and then remove the blocking group from the resulting quinoline. To obtain 5-methyl-quinoline, 2-nitro-5-methylaniline [20] and 2-carboxy-5-methylaniline [11] were converted by means of the Skraup synthesis to 5-methyl-8-nitro- and 5-methyl-8-carboxy-quinoline, respectively, and the 8 substituents then removed. In the same way toluene-2,3-diamine (2,3-diamino-toluene) [87] was converted to 7-methylquinoline by the Skraup synthesis followed by deamination of the resulting 7-methyl-8-aminoquinoline. Another method is to introduce further substituents into the two isomeric quinolines and then compare the products with compounds synthesized in an unequivocal way. Thus, the isomeric chloroquinolines obtained from *m*-chloroaniline were nitrated and the resulting products, 5-chloro-8-nitro- and 7-chloro-8-nitro-quinoline, proved to be identical with those obtained from 2-nitro-5-chloroaniline and 7-hydroxy-8-nitro-quinoline. [98, 99, 100]

The less common method for determining the identities of the 5- and 7-substituted quinolines is the synthesis of these compounds by an unambiguous method. In the Pfitzinger, Friedländer, Camps, and v. Niementowski quinoline syntheses, [9] the hetero ring is formed by linking the ends of a two-carbon chain to the amino group and the *ortho* substituent in an *ortho*-substituted aniline. The preparation of 5- and 7-substituted quinolines by these methods is therefore unequivocal. These syntheses have been frequently used to establish the identity of the 5- and 7-isomeric quinolines obtained from a *meta*-substituted aniline in the syntheses of Doebner-Miller, Conrad-Limpach-Knorr, and Combes. They may also be employed in the identification of the products of the Skraup reaction. The Pfitzinger synthesis provides 5- and 7-substituted 4-carboxyquinolines which on decarboxylation should yield the desired reference compounds.

EXPERIMENTAL CONDITIONS

Control of the Reaction

The conditions under which the earlier Skraup syntheses were carried out often resulted in reactions of uncontrollable violence. The gradual addition of one of the reagents (glycerol or sulfuric acid) does not

[20] Price and Guthrie, *J. Am. Chem. Soc.*, 68, 1592 (1946).
[11] Lutz, Bailey, Martin, and Salsbury, *J. Am. Chem. Soc.*, 68, 1324 (1946).
[100] Claus and Junghanns, *J. prakt. Chem.*, [2] 48, 254 (1893).

moderate the reaction satisfactorily, and the yields are poor. The modification of Clarke and Davis,[101] the addition of ferrous sulfate, does regulate the reaction, presumably because the ferrous sulfate functions as an oxygen carrier and therefore the reaction is extended over a longer period of time. Further improvement has been achieved by the addition of acetic [102] or boric acid.[103] Manske, Leger, and Gallagher [104] observed that the use of acetanilide in place of aniline in conjunction with ferrous sulfate and boroglyceric acid resulted in further moderation so that mole runs in 3- to 5-l. flasks could be carried out with perfect safety and increased yield. A British patent claims that the use of dilute sulfuric acid in the Skraup reaction eliminates violence and reduces the formation of tars.[105] Other workers [42, 106, 107, 108] prefer strong sulfuric acid and avoid dilution during the reaction by removal of the water formed as an azeotrope with nitrobenzene.

Though the above modifications of the original Skraup synthesis have reduced the hazards of the reaction considerably, the violence was not reduced sufficiently to permit the preparation of quinolines on a commercial scale. It was discovered recently [109] that the mode of addition of the reactants is the most important factor in controlling the vigor of the reaction. When the mixture of the aromatic amine, sulfuric acid, and glycerol kept at 80° is added in small portions to the reaction vessel containing the oxidizing agent, the reaction can be maintained easily at the required temperature and good yields can be obtained in large-scale production.

arsenic pentoxide,[43] ferric oxide or sulfate,[110] ferric chloride,[24] stannic chloride,[70, 111] chloropicrin,[112, 113] o-nitrophenol,[20] and iodine.[114]

EXPERIMENTAL PROCEDURES

The preparation of quinoline [101] in quantities of 255–275 g. with yields of 84–91%, and the preparation of 6-methoxy-8-nitroquinoline [115] in quantities of 460–540 g. with yields of 65–75%, are described in *Organic Syntheses*.

Quinoline.[104] To 20 g. of powdered crystalline ferrous sulfate in a 5-l. flask there are added with shaking, in the order named, 77.6 g. of acetanilide, 42 g. of nitrobenzene, a solution of 35.5 g. of boric acid in 216 g. of glycerol, and 182 g. of concentrated sulfuric acid. The solution is then heated gently under a reflux condenser until it begins to simmer. Careful heating is continued for one-half hour, after which time the heat is increased for a further three hours.

The solution is then cooled slightly, 300 ml. of water is added, and the mixture is steam-distilled to remove the excess nitrobenzene (about 10 g.). The residual solution is cooled, and a solution of 340 g. of sodium hydroxide in 1 l. of water is added. The alkaline mixture is steam-distilled to remove the quinoline. After the quinoline layer is separated from the distillate, the aqueous layer is distilled to recover a small additional amount of quinoline.

To the combined quinoline layers is added 70 g. of concentrated sulfuric acid, and the resulting solution is diazotized at 8° with an excess of aqueous sodium nitrite (1–2 g. is sufficient). The diazotized solution is heated on the steam bath for thirty minutes, then steam-distilled to remove volatile impurities. A solution of 100 g. of sodium hydroxide in 400 ml. of water is added to the residual solution, and the mixture is again steam-distilled. The aqueous layer in the distillate is again concentrated as described above, and the quinoline is extracted from the combined distillates by means of benzene. Removal of the benzene, followed by distillation of the residue at 110–114°/14 mm. furnishes 67 g. (90%) of water-white quinoline.

3-Ethylquinoline.[15] Into 165 g. of 20% oleum at 20–30°, 37 g. (0.3 mole) of nitrobenzene is run slowly and the mixture is heated with stirring to 60–70° over a period of approximately three hours. The

[110] Barnett, *Chem. News*, **121**, 205 (1920) [*C. A.*, **15**, 831 (1921)].

[111] Druce, *Chem. News*, **117**, 346 (1918) [*C. A.*, **13**, 289 (1919)].

[112] Gardner and Williams, Brit. pat. 198,462 [*C. A.*, **17**, 3880 (1923)].

[113] Kaufmann and Hüssy, *Ber.*, **41**, 1735 (1908).

[114] Hewitt and Trustham, U. S. pat. 2,353,162 [*C. A.*, **39**, 1421 (1945)].

[115] Mosher, Yanko, and Whitmore, *Org. Syntheses*, **27**, 48 (1947).

mixture is maintained at this temperature for an additional six to eight hours until a sample is completely soluble in water. This mixture of nitrobenzenesulfonic acid and sulfuric acid, which is termed the "sulfo mix," is poured into 50 ml. of water in a 1-l. three-necked flask, equipped with a short still head and variable-length finger condenser, a dropping funnel, a thermometer, and a stainless steel sweep stirrer. This dilutes the sulfuric acid to a concentration of 75%. With stirring, 47 g. of aniline (0.5 mole) is added; the aniline sulfate soon dissolves in the acid mixture.

The whole is heated to 125° in an oil bath, and 93 g. (0.5 mole) of α-ethylacrolein diacetate is added dropwise with stirring; the addition is momentarily stopped if the reaction becomes violent. Both during and after the addition of the acrolein acetate, the mixture is heated and stirred (stirring is momentarily stopped if excessive foaming occurs); meanwhile, the finger condenser is gradually moved up, so that a slow, steady distillation of water and acetic acid takes place. In about three hours the oil-bath temperature has been allowed to rise to 175°, about 50 ml. of distillate has come over, and distillation has almost ceased. The reaction mixture is partially cooled, poured onto about 500 g. of ice, and neutralized with concentrated sodium hydroxide solution. The crude product is removed by steam distillation, preferably with super-heated steam. The 3-ethylquinoline is separated from the distillate, with the aid of carbon tetrachloride extraction. Fractionation of the solvent-quinoline mixture gives 42.5 g. (54%) of pure 3-ethylquinoline, b.p. 265–266°; $n_D^{20} = 1.5988$.

4-Methyl-6-methoxy-8-nitroquinoline.[27] A mixture of 170 g. of arsenic acid, 50 ml. of water, 168 g. (1.0 mole) of *m*-nitro-*p*-anisidine, and 280 g. of concentrated sulfuric acid is placed in a 1-l. flask fitted with stirrer, dropping funnel, and condenser set for downward distillation. The mixture is heated in an oil bath at 110–115° while 148 g. (1.0 mole) of 1,3,3-trimethoxybutane is added dropwise in the course of two and a half hours. The mixture is stirred at 115–125° for an additional two hours while methanol distils. It is then poured into 1 l. of water, filtered, and the filtrate diluted successively to 3 and 6 l., filtering after each dilution. The precipitates (mostly tars) are discarded. The final filtrate is made basic with aqueous ammonia, and the reddish precipitate is collected and dried; the yield of crude product melting at 158–160° is about 168 g. This material is dissolved in 2–2.5 l. of 10% hydrochloric acid and the solution heated on the steam bath for fifteen minutes with Norit, then filtered. The cooled solution is neutralized with aqueous ammonia, and the dried precipitate recrystallized from 2–2.5 l. of ethyl acetate, using Norit. The mother liquors from the first crop are concen-

trated to 500 ml. to give a second crop. The total yield of material melting at 169–171° or higher is 130 g. (55–60%).

Separation of the Mixture of 3,7- and 3,5-Dimethylquinoline.[20] The mixture is prepared from *m*-toluidine and α-methylacrolein. After distillation of the mixture most of the pale greenish distillate crystallizes. The oil is drained off, and the solid 3,7-dimethylquinoline is crystallized twice from purified hexane; m.p. 80°. The oily mixture from which the solid base has crystallized is dissolved in hot dilute perchloric acid and cooled. The precipitate is collected, washed with cold water, and recrystallized from boiling water to obtain the pure perchlorate of 3,5-dimethylquinoline as brilliant colorless prisms, m.p. 216°. The 3,7-dimethylquinoline regenerated from the filtrate crystallizes at once and, after being pressed on filter paper, melts at 78°.

TABULAR SURVEY OF QUINOLINES PREPARED BY THE SKRAUP SYNTHESIS

In the tables that follow are listed the quinolines prepared by the Skraup reaction through August, 1951. Within each table the quinolines are listed according to the substituents present in the following sequence: halogen; nitro; hydroxy, alkoxy, aryloxy, and RCO_2—; sulfur-containing groups; amino; cyano; carbonyl; carboxyl; alkyl; aryl; heterocyclic. A substance containing more than one of the above groups is listed according to the group lowest in the list. Thus a 5-nitro-8-methylquinoline would follow 5,8-dicarboxyquinoline and would precede 5,8-dimethylquinoline.

TABLE I

QUINOLINES

A. Quinoline and Monosubstituted Quinolines

Quinoline	Reactants		Yield %	References
	Aniline	Second Component		
Quinoline *	Aniline	Glycerol	84–91	35, 42, 43, 70, *101*, 102, 103, 106, 107, 108, 110, 111, 112, 114, 127
	Aniline	Acrolein	70	4, 5
	N-Acetyl-	Glycerol	90	104
	N-Allyl-	Glycerol	1	135
6-Fluoro-	p-Fluoro-	Glycerol	98	184
5-Chloro-	m-Chloro-	Glycerol	22	87, 98, 187, 196
6-Chloro-	p-Chloro-	Glycerol	79	38, 145, *177*, *196*
7-Chloro-	m-Chloro-	Glycerol	68	87, 98, 187, 196
8-Chloro-	o-Chloro-	Glycerol	—	195, 196, 291
5-Bromo-	m-Bromo-	Glycerol	35	87, 190, 193
6-Bromo-	p-Bromo-	Glycerol	68	7, *177*
7-Bromo-	m-Bromo-	Glycerol	35	87, 190, 193
8-Bromo-	o-Bromo-	Glycerol	—	190, 197, 213
5-Nitro-	m-Nitro-	Glycerol	59	87, 228, 229

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

* Quinoline has been obtained in 5% yield from phenylhydroxylamine and glycerol,[118] and in traces from azoxybenzene and glycerol.[118]

TABLE I—Continued

A. Quinoline and Monosubstituted Quinolines—Continued

Quinoline	Reactants		Yield %	References
	Aniline	Second Component		
6-Nitro-	p-Nitro-	Glycerol	70	7, 43, 175, 181, 228, 238, 284
7-Nitro-	m-Nitro-	Glycerol	14	43, 87, 228, 229, 234, 235, 278
8-Nitro-	o-Nitro-	Glycerol	55	7, 43, 78, 175
5-Hydroxy-	m-Hydroxy-	Glycerol	Poor	87
6-Hydroxy-	p-Hydroxy-	Glycerol	—	12, 36
7-Hydroxy-	m-Hydroxy-	Glycerol	46	36, 38, 87, 234
8-Hydroxy-	o-Hydroxy-	Glycerol	10	36, 112, 174, 218, 226, 227
6-Methoxy-	p-Methoxy-	Glycerol	66	7, 12, 18, 90, 165, 166, 167
7-Methoxy-	m-Methoxy-	Glycerol	44	87, 169, 170
8-Methoxy-	o-Methoxy-	Glycerol	27	104, 172, 173, 174
6-Ethoxy-	p-Ethoxy-	Glycerol	53	88, 168
6-Phenoxy-	p-Phenoxy-	Glycerol	—	89
—5-sulfonic acid	—m-sulfonic acid (metanilic acid)	Glycerol	51	87, 236
—6-sulfonic acid	—p-sulfonic acid (sulfanilic acid)	Glycerol	—	37, 43, 299
—6-sulfonamide	—p-sulfonamide (sulfanilamide)	Glycerol	30	241
—6-methyl sulfone (6-SO$_2$CH$_3$)	p-Acetaminophenyl methyl sulfone	Glycerol	22	237

Quinoline	Amine	Reagent	Yield (%)	References
2-Butyl-	Aniline	HOCH(C₄H₉)CHOHCH₂OH	Poor	59
4-Butyl-	Aniline	ClCH₂CH₂COC₄H₉	40	30
3-Isobutyl-	Aniline	C₂H₅OCH₂C(C₄H₉-iso)(OH)CH₂OC₂H₅	40	21
2-Phenyl-	Aniline	C₆H₅CH=CHCHO	31	17, 18
3-Phenyl-	Aniline	C₂H₅OCH₂C(OH)(C₆H₅)CH₂OC₂H₅	12	22
4-Phenyl-	Aniline	ClCH₂CH₂COC₆H₅	53	30
6-Phenyl-	p-Phenyl-	Glycerol	—	104, 177
	p-Phenyl-N-acetyl-	Glycerol	42	201
8-Phenyl-	o-Phenyl-	Glycerol	58	201
4-p-Tolyl-	Aniline	ClCH₂CH₂COC₆H₄CH₃-p	45	30
4-(3-Methyl-6-methoxyphenyl)-	Aniline	ClCH₂CH₂CO—C₆H₃(OCH₃)(CH₃)	37	30
6-Diphenylmethyl-	p-Diphenylmethyl-Aniline	Glycerol	—	178
4-(β-Naphthyl)-	Aniline	ClCH₂CH₂COC₁₀H₇(β)	41	30
5-α-Pyridyl-	m-α-Pyridyl-	Glycerol	—	220
6-α-Pyridyl-	p-α-Pyridyl-	Glycerol	—	220
6-β-Pyridyl-	p-β-Pyridyl-	Glycerol	—	220
6-γ-Pyridyl-	p-γ-Pyridyl-	Glycerol	83	220
7-α-Pyridyl-	m-α-Pyridyl-	Glycerol	—	220
8-α-Pyridyl-	o-α-Pyridyl-	Glycerol	38	220
8-β-Pyridyl-	o-β-Pyridyl-	Glycerol	—	220
8-γ-Pyridyl-	o-γ-Pyridyl-	Glycerol	—	220
5-(2,6-Dimethyl-4-pyridyl)-	m-(2,6-Dimethyl-4-pyridyl)-	Glycerol	3	181
6-(2,6-Dimethyl-4-pyridyl)-	p-(2,6-Dimethyl-4-pyridyl)-	Glycerol	71	181
7-(2,6-Dimethyl-4-pyridyl)-	m-(2,6-Dimethyl-4-pyridyl)-	Glycerol	25	181
6-Piperidylmethyl-	p-Piperidylmethyl-	Glycerol	—	219
8-Piperidylmethyl-	o-Piperidylmethyl-	Glycerol	Poor	219
5-(or 7-) (2-Benzimidazolyl)-	m-(2-Benzimidazolyl)-	Glycerol	60	221

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE 1—*Continued*

QUINOLINES

A. Quinoline and Monosubstituted Quinolines—Continued

Quinoline	Reactants		Yield %	References
	Aniline	Second Component		
4-Methyl—(Cont'd.)	Aniline	ClCH₂CH₂COCH₃	40	*30*, 32
5-Methyl-	m-Methyl-	Glycerol	Poor	*20*, 87, 153, 154, 155
6-Methyl-	p-Methyl-	Glycerol	46	*20*, 35, *42*, 70, 112, 151, 152
7-Methyl-	m-Methyl-	Glycerol	70	*20*, 70, 87, 153, 154, 155
8-Methyl-	o-Methyl-	Glycerol	67	*20*, 35, *42*, 43, 111, 112, 155
5-Trifluoromethyl-	m-F₃C-	Glycerol	6	*156*, 263
6-Trifluoromethyl-	p-F₃C-	Glycerol	—	264
7-Trifluoromethyl-	m-F₃C-	Glycerol	32	*156*, 263
8-Trifluoromethyl-	o-F₃C-	Glycerol	—	264
6-Carboxymethyl-	p-Carboxymethyl-	Glycerol	39	290
2-Ethyl-	Aniline	HOCH(C₂H₅)CHOHCH₂OH	Poor	59
3-Ethyl-	Aniline	C₂H₅OCH₂C(C₂H₅)OHCH₂OC₂H₅	40	*21*, 22, 23
	Aniline	CH₂=C(C₂H₅)CHO	42	15
	Aniline	CH₂=C(C₂H₅)CH(OCOCH₃)₂	54	15
4-Ethyl-	Aniline	ClCH₂CH₂COC₂H₅	40	*30*, 31, 32
7-Ethyl-	m-Ethyl-	Glycerol	92	20
8-Ethyl-	o-Ethyl-	Glycerol	50	158
2-Propyl-	Aniline	HOCH(C₃H₇)CHOHCH₂OH	Poor	59
3-Propyl-	Aniline	C₂H₅O(CH₂OH)₃	15	23
4-Propyl-	Aniline	ClCH₂CH₂COC₃H₇	40	30
8-Propyl-	o-Propyl-	Glycerol	35	163

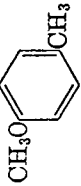|			Yield (%)	References
5,7-Dinitro-	3,5-Dinitro-	Glycerol	—	113
6,8-Dinitro-	2,4-Dinitro-	Glycerol	63	113, 177, *308*
7,8-Dinitro-	2,3-Dinitro-	Glycerol	—	113
5-Chloro-6-hydroxy-	5-Chloro-4-hydroxy-	Glycerol	30	218
5-Chloro-8-hydroxy-	5-Chloro-2-hydroxy-	Glycerol	35	*218*, 231, 270
6-Chloro-8-hydroxy-	4-Chloro-2-hydroxy-	Glycerol	50	286
5-Nitro-8-hydroxy-	5-Nitro-2-hydroxy-	Glycerol	2	80, *255*
6,8-Dihydroxy-	2,4-Dihydroxy-	Glycerol	—	134
5-Chloro-8-methoxy-	5-Chloro-2-methoxy-	Glycerol	40	270
7-Bromo-6-methoxy-	5-Bromo-4-methoxy-	Glycerol	58	92
8-Bromo-6-methoxy-	3-Bromo-4-methoxy-	Glycerol	—	92
7-Bromo-6-ethoxy-	3-Bromo-4-ethoxy-	Glycerol	—	92
5-Nitro-6-methoxy-	3-Nitro-4-methoxy-	Glycerol	—	297
5-Nitro-8-methoxy-	5-Nitro-2-methoxy-	Glycerol	59	7, 173
6-Nitro-8-methoxy-	4-Nitro-2-methoxy-	Acrolein	87	*120*, 263, 266, 284
	4-Nitro-2-methoxy-	Glycerol	67	7
	4-Nitro-2-methoxy-	Acrolein		
7-Nitro-6-methoxy-	3-Nitro-4-methoxy-	Glycerol	—	297
8-Nitro-6-methoxy-	2-Nitro-4-methoxy-	Glycerol	76	6, 75, *115*, 116, 117, 118, 119, 120, 232, 248, 284
	2-Nitro-4-methoxy-	Acrolein	60	7
8-Nitro-6-ethoxy-	2-Nitro-4-ethoxy-	CH$_2$=C(Br)CHO	68	321
8-Nitro-6-(γ-aminopropoxy)-	2-Nitro-4-(γ-phthalimido-propoxy)-	Glycerol	71	115, *117*, 118, 239
		Glycerol	70	123
8-Nitro-6-butoxy-	2-Nitro-4-butoxy-	Glycerol	28	122
8-Nitro-6-phenoxy-	2-Nitro-4-phenoxy-	Glycerol	30	249
6,7-Dimethoxy-	3,4-Dimethoxy-	Glycerol	83	91, *93*, 307
7,8-Dimethoxy-	2,3-Dimethoxy-	Glycerol	58	294

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE I—Continued

QUINOLINES

Quinoline	Aniline	Second Component	Yield %	References
A. Quinoline and Monosubstituted Quinolines—Continued				
6-(2-Benzimidazolyl)-		Glycerol	40	221
8-(2-Benzimidazolyl)-		Glycerol	50	221, 224
6-(6-Methyl-2-benzothiazolyl)-		Glycerol	15	223
B. Disubstituted Quinolines				
5,7-Dichloro-	3,5-Dichloro-	Glycerol	80–90	129
5,8-Dichloro-	2,5-Dichloro-	Glycerol	83	5, 38, 177
6,8-Dichloro-	2,4-Dichloro-	Glycerol	35	38, 269
5,6-Dibromo-	3,4-Dibromo-	Glycerol	Good	130
5,7-Dibromo-	3,5-Dibromo-	Glycerol	—	128
5,8-Dibromo-	2,5-Dibromo-	Glycerol	—	130
6,7-Dibromo-	3,4-Dibromo-	Glycerol	—	130
6,8-Dibromo-	2,4-Dibromo-	Glycerol	46	184
6-Fluoro-8-nitro-	4-Fluoro-2-nitro-	Glycerol	20	99, 196
5-Chloro-6-nitro-	3-Chloro-4-nitro-	Glycerol	50	99, 196
5-Chloro-8-nitro-	5-Chloro-2-nitro-	Glycerol	—	196
6-Chloro-7-nitro-	4-Chloro-3-nitro-	Glycerol	90	79, 115, 120, 247
6-Chloro-8-nitro-	4-Chloro-2-nitro-	Glycerol	35	99, 196
7-Chloro-6-nitro-	3-Chloro-4-nitro-	Glycerol	—	196
8-Chloro-5-nitro-	2-Chloro-5-nitro-	Glycerol	—	38
8-Chloro-6-nitro-	2-Chloro-4-nitro-	Glycerol	91	79
6-Bromo-8-nitro-	4-Bromo-2-nitro-	Glycerol	60	131
8-Bromo-6-nitro-	2-Bromo-4-nitro-	Glycerol	40	113
5,6-Dinitro-	3,4-Dinitro-	Glycerol		

Product	Amine	Reagent	Yield (%)	References
5,7-Dinitro-	3,5-Dinitro-	Glycerol	—	113
6,8-Dinitro-	2,4-Dinitro-	Glycerol	63	113, 177, *308*
7,8-Dinitro-	2,3-Dinitro-	Glycerol	—	113
5-Chloro-6-hydroxy-	5-Chloro-4-hydroxy-	Glycerol	30	218
5-Chloro-8-hydroxy-	5-Chloro-2-hydroxy-	Glycerol	35	*218*, 231, 270
6-Chloro-8-hydroxy-	4-Chloro-2-hydroxy-	Glycerol	50	286
5-Nitro-8-hydroxy-	5-Nitro-2-hydroxy-	Glycerol	2	80, *255*
6,8-Dihydroxy-	2,4-Dihydroxy-	Glycerol	—	134
5-Chloro-8-methoxy-	5-Chloro-2-methoxy-	Glycerol	40	270
7-Bromo-6-methoxy-	3-Bromo-4-methoxy-	Glycerol	58	92
8-Bromo-6-methoxy-	2-Bromo-4-methoxy-	Glycerol	—	92
7-Bromo-6-ethoxy-	3-Bromo-4-ethoxy-	Glycerol	—	92
5-Nitro-6-methoxy-	3-Nitro-4-methoxy-	Glycerol	—	297
5-Nitro-8-methoxy-	5-Nitro-2-methoxy-	Acrolein	59	7, 173
6-Nitro-8-methoxy-	4-Nitro-2-methoxy-	Glycerol	87	*120*, 263, 266, 284
	4-Nitro-2-methoxy-	Acrolein	67	7
7-Nitro-6-methoxy-	3-Nitro-4-methoxy-	Glycerol	—	297
8-Nitro-6-methoxy-	2-Nitro-4-methoxy-	Glycerol	76	6, 75, *115*, 116, 117, 118, 119, 120, 232, 248, 284
	2-Nitro-4-methoxy-	Acrolein	60	7
8-Nitro-6-ethoxy-	2-Nitro-4-ethoxy-	CH$_2$=C(Br)CHO	68	321
8-Nitro-6-(γ-aminopropoxy)-	2-Nitro-4-(γ-phthalimido-propoxy)-	Glycerol	71	115, *117*, 118, 239
		Glycerol	70	123
8-Nitro-6-butoxy-	2-Nitro-4-butoxy-	Glycerol	28	122
8-Nitro-6-phenoxy-	2-Nitro-4-phenoxy-	Glycerol	30	249
6,7-Dimethoxy-	3,4-Dimethoxy-	Glycerol	83	*91*, 93, 307
7,8-Dimethoxy-	2,3-Dimethoxy-	Glycerol	58	294

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE I—*Continued*

QUINOLINES

B. Disubstituted Quinolines—Continued

Quinoline	Aniline	Second Component	Yield %	References
6,7-Methylenedioxy-	3,4-Methylenedioxy-	Glycerol	Poor	88, 307
6,7-Ethylenedioxy-	3,4-Ethylenedioxy-	Glycerol	62	88, 89
6,7-Phenylenedioxy-	3,4-Phenylenedioxy-	Glycerol	—	89
6-Methoxy-8-(1-diethylamino-1-pentylamino)-	4-Methoxy-2-(1-diethylamino-1-pentylamino)-	Glycerol	—	295
8-Chloro-5-sulfonic acid	2-Chloro-5-sulfonic acid	Glycerol		132
8-Chloro-5-carboxy-	2-Chloro-5-carboxy-	Glycerol	83	258
8-Bromo-5-carboxy-	2-Bromo-5-carboxy-	Glycerol	—	179
5-Nitro-8-carboxy-	5-Nitro-2-carboxy-	Glycerol	70	87
8-Hydroxy-5-carboxy-	2-Hydroxy-5-carbomethoxy-	Glycerol	29	126
8-Hydroxy-6-carboxy-	2-Hydroxy-4-carbomethoxy-	Glycerol	65	126
5-Methoxy-8-carboxy-	5-Methoxy-2-carboxy-	Glycerol	20	87
6-Methoxy-8-carboxy-	4-Methoxy-2-carbomethoxy-	Glycerol	—	256, 296
5,8-Dicarboxy-	2,5-Dicarboxy-	Glycerol	—	153
5-Chloro-4-methyl-	m-Chloro-	$CH_3C(OCH_3)_2CH_2CH_2OCH_3$	—	25
6-Chloro-2-methyl-	p-Chloro-	$CH_3CH=CHCH(OCOCH_3)_2$	55	15, 244
6-Chloro-4-methyl-	p-Chloro-	$CH_3C(OCH_3)_2CH_2CH_2OCH_3$	55	32, 33
6-Chloro-8-methyl-	2-Methyl-4-chloro-	Glycerol	—	161
7-Chloro-2-methyl-	m-Chloro-	Crotonaldehyde	60	15
7-Chloro-3-methyl-	m-Chloro-	$CH_3CH(OCH_3)CH_2CH(OCH_3)_2$	30	16
7-Chloro-4-methyl-	m-Chloro-	$CH_2=C(CH_3)CH(OCOCH_3)_2$	52	15
7-Chloro-8-methyl-	m-Chloro-	$CH_3C(OCH_3)_2CH_2CH_2OCH_3$	67	25
8-Chloro-2-methyl-	3-Chloro-2-methyl-	Glycerol	74	87
	o-Chloro-	$CH_3CH=CHCHO$	—	151, 244

Product	Amine	Reagent	Yield (%)	References
8-Chloro-4-methyl-	o-Chloro-	$CH_3C(OCH_3)_2CH_2CH_2OCH_3$	23	24
8-Chloro-5-methyl-	2-Chloro-5-methyl-	Glycerol	62	121, *273*
5-Bromo-8-methyl-	5-Bromo-2-methyl-	Glycerol	—	275
6-Bromo-3-methyl-	p-Bromo-	$CH_2{=}C(CH_3)CHO$	13	20
6-Bromo-8-methyl-	4-Bromo-2-methyl-	Glycerol	95	161, *277*
7-Bromo-8-methyl-	3-Bromo-2-methyl-	Glycerol	—	275
8-Bromo-6-methyl-	2-Bromo-4-methyl-N-acetyl-	Glycerol	36	309
5-(or 7-)Nitro-6-methyl-	3-Nitro-4-methyl-	Glycerol	53	280, 281
5-Nitro-8-methyl-	5-Nitro-2-methyl-	Glycerol	—	280
6-Nitro-2-methyl-	p-Nitro-	$CH_3CH{=}CHCH(OCOCH_3)_2$	30	15
6-Nitro-3-methyl-	p-Nitro-	$CH_2{=}C(CH_3)CH(OCOC_2H_5)_2$	35	15
6-Nitro-1-methyl-	p-Nitro-	$CH_3COCH_2CH_2Cl$	20	31, 32, *298*
6-Nitro-5-methyl-	4-Nitro-3-methyl-	Glycerol	7	50
6-Nitro-7-methyl-	4-Nitro-3-methyl-	Glycerol	35	50
6-Nitro-8-methyl-	4-Nitro-2-methyl-	Glycerol		
7-Nitro-8-methyl-	3-Nitro-2-methyl-	Glycerol	—	287
8-Nitro-3-methyl-	o-Nitro-	Glycerol	—	319
8-Nitro-5-methyl-	2-Nitro-5-methyl-	$CH_2{=}C(CH_3)CH(OCOCH_3)_2$	43	315
8-Nitro-6-methyl-	2-Nitro-4-methyl-	Glycerol	23	20, *246*
8-Nitro-7-methyl-	2-Nitro-3-methyl-	Glycerol	81	*79*, 151, 280
8-Hydroxy-2-methyl-	o-Hydroxy-	$CH_3CH{=}CHCHO$	43	*246*, 259
8-Hydroxy-5-methyl-	2-Hydroxy-5-methyl-	Glycerol	—	279
8-Hydroxy-3-methyl-	2-Hydroxy-3-methyl-	Glycerol	65	280
8-Hydroxy-5-t-octyl-	2-Hydroxy-5-t-octyl-	Glycerol	80	280
6-Methoxy-2-methyl-	p-Methoxy-	$CH_3CH{=}CHCHO$	45	306
6-Methoxy-1-methyl-	p-Methoxy-	$CH_3COCH_2CH_2Cl$	—	16
6-Methoxy-8-methyl-	4-Methoxy-2-methyl-	$CH_3COCH{=}CH_2$	52	31, 32
8-Methoxy-1-methyl-	o-Methoxy-	Glycerol	24	24
6-Ethoxy-1-methyl-	p-Ethoxy-	$CH_3COCH_2CH_2Cl$	43	267
		$CH_3COCH_2CH_2Cl$	—	31, 32
		$CH_3COCH_2CH_2Cl$	—	31, 32

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE I—Continued

QUINOLINES

Quinoline	Reactants		Yield %	References
	Aniline	Second Component		
B. Disubstituted Quinolines—Continued				
6-Methyl—7-sulfonic acid	4-Methyl—3-sulfonic acid	Glycerol	37	289
6-Methyl—8-sulfonic acid	4-Methyl—2-sulfonic acid	Glycerol	83	292
9-Methyl—5-sulfonic acid	2-Methyl—5-sulfonic acid	Glycerol	83	293
8-Methyl—6-sulfonic acid	2-Methyl—4-sulfonic acid	Glycerol	83	287, 293
6-Arsonamino-2-methyl-	p-Arsonamino-(arsanilic acid)	$CH_3CH{=}CHCHO$	—	136
8-Amino-7-methyl-	2-Amino-3-methyl-	Glycerol	22	87
6-Carboxy-2-methyl-	p-Carboxy-	$CH_3CH{=}CHCHO$	—	244
8-Carboxy-4-methyl-	o-Carboxy-	$CH_3COCH_2CH_2Cl$	—	31, 32
3-Carboxy-5-methyl-	2-Cyano-5-methyl-	Glycerol	70	11, 87
8-Carboxy-6-methyl-	2-Cyano-4-methyl-	Glycerol	70	272
2-Phenyl—6-sulfonic acid	—4-sulfonic acid (sulfanilic acid)	$C_6H_5CH{=}CHCHO$	—	211
2,4-Dimethyl-	Aniline	$CH_3COCH_2CHOHCH_3$	18	20, 209
	Aniline	$CH_3COCH{=}CHCH_3$	62	24
2,6-Dimethyl-	p-Methyl-	$CH_3CH{=}CHCH(OCOC_2H_5)_2$	49	15
2,7-Dimethyl-	m-Methyl-	$CH_3CH{=}CHCHO$	62	15
	m-Methyl-	$CH_3CH{=}CHCH(OCOCH_3)_2$	47	15
2,8-Dimethyl-	o-Methyl-	$CH_3CH{=}CHCHO$	—	244
3,4-Dimethyl-	Aniline	$CH_3COCH(CH_3)CH_2OH$	42	20
3,5-Dimethyl-	m-Methyl-	$CH_2{=}C(CH_3)CHO$	—	20
3,6-Dimethyl-	p-Methyl-	$CH_2{=}C(CH_3)CHO$	12	20
	p-Methyl-	$CH_2{=}C(CH_3)CH(OCOCH_3)_2$	54	15
3,7-Dimethyl-	m-Methyl-	$CH_2{=}C(CH_3)CHO$	65	15, 20
3,8-Dimethyl-	o-Methyl-	$CH_2{=}C(CH_3)CH(OCOCH_3)_2$	45	15

3,8-Dimethyl-*Continued*	o-Methyl-	CH$_2$=C(CH$_3$)CHO	18	20
4,6-Dimethyl-	p-Methyl-	CH$_3$COCH=CH$_2$	65	24
	p-Methyl-	CH$_3$COCH$_2$CH$_2$OH	—	29
5,6-Dimethyl-	3,4-Dimethyl-	Glycerol	Poor	20
5,7-Dimethyl-	3,5-Dimethyl-	Glycerol	39	*20*, 253
5,8-Dimethyl-	2,5-Dimethyl-	Glycerol	—	*20*, 112, 179
6,7-Dimethyl-	3,4-Dimethyl-	Glycerol	67	*20*, 245
6,8-Dimethyl-	2,4-Dimethyl-	Glycerol	70	*20*, 261, 262
7,8-Dimethyl-	2,3-Dimethyl-	Glycerol	50	20
6-Nitro-7-ethyl-	4-Nitro-3-ethyl-	Glycerol	43	288
6-Methyl-3-ethyl-	p-Methyl-	CH$_2$=C(C$_2$H$_5$)CH(OCOCH$_3$)$_2$	32	15
7-Methyl-3-ethyl-	m-Methyl-	CH$_2$=C(C$_2$H$_5$)CHO	35	15
8-Methyl-6-ethyl-	2-Methyl-4-ethyl-	Glycerol	—	265
6-Methoxyl-4-propyl-	p-Methoxy-	CH$_3$CH$_2$CH$_2$COCH$_2$CH$_2$Cl	20	285
8-Methyl-5-isopropyl-	2-Methyl-5-isopropyl-	Glycerol	27	257, *276*
6-Methoxy-8-isoamyl-	4-Methoxy-2-isoamyl-	Glycerol	—	268
8-Nitro-2-phenyl-	o-Nitro-	C$_6$H$_5$CH=CHCHO	15	19
8-Nitro-4-phenyl-	o-Nitro-	C$_6$H$_5$COCH$_2$CH$_2$Cl	45	282
8-Nitro-5-phenyl-	2-Nitro-5-phenyl-N-acetyl-	Glycerol	50	282
8-Nitro-6-phenyl-	2-Nitro-4-phenyl-N-acetyl-	Glycerol	40	282
8-Hydroxy-5-phenyl-	2-Hydroxy-5-phenyl-	Glycerol	95	125
8-Hydroxy-7-phenyl-	2-Hydroxy-3-phenyl-	Glycerol	61	125
2-Carboxy-4-phenyl-	Aniline	C$_6$H$_5$COCH=CHCO$_2$H	15–20	212
8-Hydroxy-5-benzyl-	2-Hydroxy-5-benzyl-	Glycerol	86	124
8-Nitro-6-α-pyridyl-	2-Nitro-4-α-pyridyl-	Glycerol	32	133
8-Hydroxy-5-α-pyridyl-	2-Hydroxy-5-α-pyridyl-	Glycerol	40	90
6-Methoxy-5-α-pyridyl-	4-Methoxy-3-α-pyridyl-	Glycerol	—	90
6-Methoxy-7-α-pyridyl-	4-Methoxy-3-α-pyridyl-	Glycerol	—	90
6-Methoxy-8-α-pyridyl-	4-Methoxy-2-α-pyridyl-	Glycerol	—	90
6-Methoxy-2-α-pyridyl-	4-Methoxy-2-α-pyridyl-	Glycerol	—	90
6-Methoxy-8-β-pyridyl-	4-Methoxy-2-β-pyridyl-	Glycerol	—	90

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE I—*Continued*

QUINOLINES

	Reactants		Yield %	References
Quinoline	Aniline	Second Component		
B. Disubstituted Quinolines—Continued				
6-Methoxy-8-γ-pyridyl-	4-Methoxy-2-γ-pyridyl-	Glycerol	—	90
8-Methoxy-5-α-pyridyl-	2-Methoxy-5-α-pyridyl-	Glycerol	65	90
5-t-Butyl-8-pyridyl-†	5-t-Butyl-2-pyridyl-	Glycerol	60	90
5,8-Dipyridyl-†	2,5-Dipyridyl-	Glycerol	60	133
6,8-Dipyridyl-†	2,4-Dipyridyl-	Glycerol	40	133
C. Trisubstituted Quinolines				
5,6,7-Trichloro-	3,4,5-Trichloro-	Glycerol	—	38
5,6,8-Trichloro-	2,4,5-Trichloro-	Glycerol	—	38
6,8-Dichloro-5-nitro-	2,4-Dichloro-5-nitro-	Glycerol	50	269
5,7-Dichloro-8-hydroxy-	3,5-Dichloro-2-hydroxy-	Glycerol	35	218
3-Bromo-6-chloro-8-nitro-	2-Nitro-4-chloro-	$BrCH_2CBr_2CHO$	—	321
3,6-Dibromo-8-nitro-	2-Nitro-4-bromo-	$CH_2{=}CBrCH(OCOCH_3)_2$	38	316
5,6-Dibromo-8-nitro-	2-Nitro-4,5-dibromo-	Glycerol	29	316
5-Fluoro-8-nitro-6-methoxy-	5-Fluoro-2-nitro-4-methoxy-	Glycerol	5	13
3-Chloro-8-nitro-6-methoxy-	2-Nitro-4-methoxy-	$CH_2{=}CClCHO$	25	8
3-Bromo-8-nitro-6-methoxy-	2-Nitro-4-methoxy-	$BrCH_2CBr_2CHO$	73	321
5-Chloro-8-nitro-6-methoxy-	5-Chloro-2-nitro-4-methoxy-	Glycerol	—	146, 160
5-Bromo-8-nitro-6-methoxy-	5-Bromo-2-nitro-4-methoxy-	Glycerol	45	115, 250
6-Chloro-5-nitro-8-methyl-	4-Chloro-2-methyl-5-nitro-	Glycerol	9	161
6-Bromo-5-nitro-8-methyl-	4-Bromo-2-methyl-5-nitro-	Glycerol	20	161
8-Bromo-5-nitro-6-methyl-	2-Bromo-4-methyl-5-nitro-	Glycerol	7	309
8-Nitro-5-hydroxy-6-methoxy-	2-Nitro-5-fluoro-4-methoxy-	Glycerol	54	13

Quinoline	Amine	Other Reactant	Yield (%)	References
5-Bromo-6,7-dimethoxy-	5-Bromo-3,4-dimethoxy-	Glycerol	15	75
8-Nitro-5,6-dimethoxy-	2-Nitro-4,5-dimethoxy-	Glycerol	40	6, *18*, 251
8-Nitro-5,6-methylenedioxy-	2-Nitro-4,5-methylenedioxy-	Acrolein	50	318
8-Nitro-5,6-ethylenedioxy-	2-Nitro-4,5-ethylenedioxy-	Acrolein	53	318
6,7,8-Trimethoxy-	2,3,4-Trimethoxy-	Glycerol	—	144, 307
5-Bromo-6-methoxy-8-methyl-	5-Bromo-4-methoxy-2-methyl-	Glycerol	—	267
7-Bromo-6-methoxy-8-methyl-	3-Bromo-4-methoxy-2-methyl-	Glycerol	—	267
8-Nitro-6-methoxy-2-methyl-	2-Nitro-4-methoxy-	$CH_3CH{=}CHCHO$	36	252
8-Nitro-6-methoxy-4-methyl-	2-Nitro-4-methoxy-	$CH_3OCH_2CH_2C(OCH_3)_2CH_3$	60	26, *27*
8-Nitro-6-methoxy-5-methyl-	2-Nitro-4-methoxy-5-methyl-	Glycerol	57	254
7-Amino-8-methyl—5-sulfonic acid	3-Amino-2-methyl—5-sulfonic acid	Glycerol	—	143
7-Amino-5-carboxy-8-methyl-	3-Amino-5-carboxy-2-methyl-	Glycerol	—	143
5-Nitro-6,8-dimethyl-	5-Nitro-2,4-dimethyl-	Glycerol	—	280
6-Nitro-5,8-dimethyl-	4-Nitro-2,5-dimethyl-	Glycerol	50	50
6-Nitro-7,8-dimethyl-	4-Nitro-2,3-dimethyl-	Glycerol	50	298
7-Nitro-5-isopropyl-8-methyl-	3-Nitro-2-methyl-5-isopropyl-	Glycerol	—	319
8-Nitro-3,4-dimethyl-	o-Nitro-	$CH_3COCH(CH_3)CH_2OH$	30	271
8-Nitro-3,5-dimethyl-	2-Nitro-5-methyl-	$CH_2{=}C(CH_3)CH(OCOCH_3)_2$	28	20, *317*
8-Nitro-3,6-dimethyl-	2-Nitro-4-methyl-	$CH_2{=}C(CH_3)CH(OCOCH_3)_2$	34	317
8-Nitro-4,5-dimethyl-	2-Nitro-5-methyl-	$CH_3COCH_2CH_2OH$	9	20, *317*
8-Nitro-4,6-dimethyl-	2-Nitro-4-methyl-	$CH_3COCH{=}CH_2$	36	317

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

† The point of attachment to the pyridine ring was not reported.

TABLE I—*Continued*

QUINOLINES

Quinoline	Reactants		Yield %	References
	Aniline	Second Component		
	C. Trisubstituted Quinolines—Continued			
8-Nitro-5,6-dimethyl-	2-Nitro-4,5-dimethyl-	Glycerol	63	20, *315*
6-Methoxy-5,7-dimethyl-	4-Methoxy-3,5-dimethyl-	Glycerol	28	122
6-Amino-5,8-dimethyl-	4-Amino-2,5-dimethyl-	Glycerol	—	140
		Glycerol	—	141
5,8-Dimethyl—6-sulfonic acid	2,5-Dimethyl—4-sulfonic acid	Glycerol	—	141, 142
5,8-Dimethyl—7-sulfonic acid	2,5-Dimethyl—3-sulfonic acid	Glycerol	27	20
3,4,7-Trimethyl-	m-Methyl-	CH₃COCH(CH₃)CH₂OH	Good	138, *180*
2,4,5-Trimethyl-	m-Methyl-	Glycerol	18	298
5,6,8-Trimethyl-	2,4,5-Trimethyl-	CH₃CH₂COCH₂CH₂Cl	39	298
6-Nitro-7-methyl-4-ethyl-	4-Nitro-3-methyl-	CH₃CH₂COCH₂CH₂Cl	8	19
6-Nitro-8-methyl-4-ethyl-	4-Nitro-2-methyl-	C₆H₅CH=OHCHO	30	312
8-Nitro-6-methoxy-2-phenyl-	2-Nitro-4-methoxy-	C₆H₅COCH₂CH₂Cl	37	243
8-Nitro-6-methoxy-4-phenyl-	2-Nitro-4-methoxy-	Glycerol		
8-Nitro-6-methoxy-5-phenyl-	2-Nitro-4-methoxy-5-phenyl-	C₆H₅COCH₂CH₂Cl	50	282
8-Nitro-4,6-diphenyl-	2-Nitro-4-phenyl-			
	D. Tetrasubstituted Quinolines			
8-Nitro-3,5,6-tribromo-	2-Nitro-4,5-dibromo-N-acetyl-	CH₂=C(Br)CH(OCOCH₃)₂	24	316
8-Nitro-3,4,6-trimethyl-	2-Nitro-4-methyl-	CH₃COCH(CH₃)CH₂OH	17	271
8-Nitro-3,5,6-trimethyl-	2-Nitro-4,5-dimethyl-	CH₂=C(CH₃)CH(OCOCH₃)₂	65	315

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE II

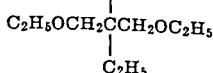### BENZOQUINOLINES

A. Benzo(h)quinolines

Benzo(h)quinoline (ring structure: N 1,2,3,4,5,6,7,8,9,10)
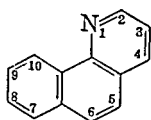
	Reactants		Yield	
	1-Naphthylamine	Second Component	%	References
Benzo(h)quinoline	1-Naphthylamine	Glycerol	25	35, 36, 39, *40*
7,8,9,10-Tetra-hydro-	5,6,7,8-Tetra-hydro-	Glycerol	—	149
6-Hydroxy-7,8,9,10-tetrahydro-	4-Hydroxy-5,6,7,8-tetrahydro-	Glycerol	25–30	260
—7-sulfonic acid	—5-sulfonic acid	Glycerol		
—10-sulfonic acid	—8-sulfonic acid	Glycerol	—	37, 38
6-Methyl-	4-Methyl-	Glycerol	60	41
			—	230
3-Ethyl-	1-Naphthylamine	$C_2H_5OCH_2\underset{\underset{C_2H_5}{\vert}}{\overset{\overset{OH}{\vert}}{C}}CH_2OC_2H_5$	12	22
6,7-Ace-	4,5-Ace-	Glycerol	35	58

B. Benzo(f)quinolines
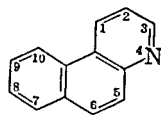
Benzo(f)quinoline (ring structure: N 4,3,2,1,10,9,8,7,6,5)

	Reactants		Yield	
	2-Naphthylamine	Second Component	%	References
Benzo(f)quinoline	2-Naphthylamine	Glycerol	81	36, 42, 43, 44, 45, *46*, 47, 48, 49, 216
7,8,9,10-Tetra-hydro-	5,6,7,8-Tetra-hydro-	Glycerol	19	53
10-Chloro-	1,8-Dichloro-	Glycerol		
10-Bromo-	1-Chloro-8-bromo-	Glycerol	15	283
8-Nitro-	6-Nitro-	Glycerol	38	52
10-Nitro-	8-Nitro-	Glycerol	34	46
—8-sulfonic acid	—6-sulfonic acid	Glycerol	34	46
—10-sulfonic acid	—8-sulfonic acid	Glycerol	—	38
5-Carboxy-	3-Carboxy-	Glycerol	—	159
6-Carboxy-	4-Carboxy-	Glycerol	29	242
1-Methyl-	2-Naphthylamine	$CH_3OCH_2CH_2C(OCH_3)_2CH_3$	—	157
3-Methyl-	2-Naphthylamine	$CH_3CH{=}CHCHO$	53	*24*, 215
10-Hydroxy—8-sulfonic acid	8-Hydroxy—6-sulfonic acid	Glycerol	—	244
			—	28, 162

Note: References 116–322 are listed on pp. 94–95. Where one reference is italicized, the yield reported is taken from that reference.

TABLE II—*Continued*

BENZOQUINOLINES

C. Benzo(g)quinolines
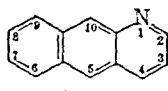
	Reactants		Yield	
	2-Naphthylamine	Second Component	%	References
6,7,8,9-Tetrahydro-	5,6,7,8-Tetrahydro-	Glycerol	36	53
10-Chloro-	1-Chloro-	Glycerol	34	51, 52
10-Methyl-	1-Methyl-	Glycerol	25	50
6,10-Dichloro-	1,5-Dichloro-	Glycerol	—	283
5,10-Dichloro-	1,4-Dichloro-	Glycerol	—	283
10-Chloro-6-bromo-	1-Chloro-5-bromo-	Glycerol	—	52
10-Chloro-6-nitro-	1-Chloro-5-nitro-	Glycerol	—	51
10-Chloro-7-nitro-	1-Chloro-6-nitro-	Glycerol	4	*51*, 52
10-Chloro-9-nitro-	1-Chloro-8-nitro-	Glycerol	12	51
5,10-Diphenyl-	1,4-Diphenyl-	Glycerol	40–50	233
9-Hydroxy—7-sul- fonic acid	8-Hydroxy—6-sul- fonic acid	Glycerol	—	162

Note: References 116–322 are listed on pp. 94–98   Where one reference is italicized, the yiel reported is taken from that reference.

TABLE III

Biquinolyls

Biquinolyls are numbered to show the carbon atoms through which the two quinoline nuclei are joined; e.g., 2,7'-biquinolyl is
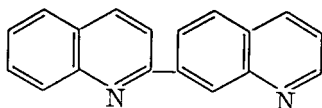
| Biquinolyl | Reactants | | Yie'd % | References |
	Amine	Second Component		
2,5'-	2-*m*-Aminophenyl-quinoline	Glycerol	21	189
2,7'-	2-*m*-Aminophenyl-quinoline	Glycerol	30	*189, 225*
4,6'-	4-*p*-Aminophenyl-quinoline	Glycerol	—	188
4,7'-	4-*m*-Aminophenyl-quinoline	Glycerol	—	188
6,6'-	4,4'-Diaminobiphenyl	Glycerol	80	83, *84, 85*, 198
6,8'-	2,4'-Diaminobiphenyl	Glycerol	50	199
8,8'-	2,2'-Diaminobiphenyl	Glycerol	65	200
6-Methoxy-2,5'-	2-*m*-Aminophenyl-6-methoxyquinoline	Glycerol	21	191
6-Methoxy-2,7'-	2-*m*-Aminophenyl-6-methoxyquinoline	Glycerol	32	191
2'-(*p*-Nitrophenyl)-2,6'-	2-*p*-Aminophenyl-quinoline	*p*-NO$_2$C$_6$H$_4$CH=CHCHO	6	301
4-Methyl-2,6'-	2-*p*-Aminophenyl-4-methylquinoline	Glycerol	—	86
8,8'-Dihydroxy-5,5'-	3,3'-Diamino-4,4'-dihydroxybiphenyl	Glycerol	35	206
5,5'-Dicarboxy-8,8'-	2,2'-Diamino-4,4'-dicarboxybiphenyl	Glycerol	79	205
2,2'-Dimethyl-6,6'-	4,4'-Diaminobiphenyl	Crotonaldehyde	—	244
5,5'-Dimethyl-8,8'-	2,2'-Diamino-4,4'-dimethylbiphenyl	Glycerol	60	200

Note: References 116–322 are listed on pp. 91–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE V

PHENANTHROLINES

A. 1,10-Phenanthrolines

Phenanthroline

Phenanthroline	Reactants		Yield %	References
	Amine	Second Component		
1,10-Phenanthroline	o-Phenylenediamine	Glycerol	45	76
	8-Aminoquinoline	Glycerol	40	71, 78
(5)6-Chloro-1,10-	6-Chloro-8-aminoquinoline	Glycerol	56	79
3-Bromo-1,10-	8-Amino-3-bromoquinoline	Glycerol	20	316
(5)6-Bromo-1,10-	5-Bromo-8-aminoquinoline	Glycerol	40	76
	6-Bromo-8-aminoquinoline	Glycerol	46	79
(5)6-Nitro-1,10-	5-Nitro-8-aminoquinoline	Glycerol	—	76
2-Methyl-1,10-	2-Methyl-8-aminoquinoline	Glycerol	—	183
3-Methyl-1,10-	8-Aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	6	315
4-Methyl-1,10-	8-Amino-4-methylquinoline	Glycerol	15	315
5(6)-Methyl-1,10-	8-Amino-6-methylquinoline	Glycerol	66	79
4-Phenyl-1,10-	8-Aminoquinoline	$C_6H_5COCH_2CH_2Cl$	15	282
	4-Phenyl-8-aminoquinoline	Glycerol	Poor	282
5(6)-Phenyl-1,10-	6-Phenyl-8-aminoquinoline	Glycerol	20	282
3,5-Dibromo-1,10-	8-Amino-6-bromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	1.4	316
3,6-Dibromo-1,10-	8-Amino-3,6-dibromoquinoline	Glycerol	28	316
3,8-Dibromo-1,10-	8-Amino-3-bromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	5	316
5,6-Dibromo-1,10-	8-Amino-5,6-dibromoquinoline	Glycerol	14	316
7-Chloro-3-methyl-1,10-	8-Amino-4-chloroquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	3	315
2-Hydroxy-4-methyl-1,10-	8-Amino-2-hydroxy-4-methylquinoline	Glycerol	20–30	80
2,9-Dimethyl-1,10-	8-Aminoquinaldine	Crotonaldehyde diacetate	7	315
3,4-Dimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	Glycerol	22	271
3,5-Dimethyl-1,10-	8-Amino-6-methylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	4	317
3,6-Dimethyl-1,10-	8-Amino-3,6-dimethylquinoline	Glycerol	3	317
3,7-Dimethyl-1,10-	8-Amino-4-methylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	2	315
3,8-Dimethyl-1,10-	8-Amino-3-methylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	315
4,5-Dimethyl-1,10-	8-Amino-4,5-dimethylquinoline	Glycerol	24	317
4,6-Dimethyl-1,10-	8-Amino-4,6-dimethylquinoline	Glycerol	11	317
4,7-Dimethyl-1,10-	8-Amino-4-methylquinoline	$CH_3OCH_2CH_2C(OCH_3)_2CH_3$	7	315
5,6-Dimethyl-1,10-	8-Amino-5,6-dimethylquinoline	Glycerol	9	315
4,6-Diphenyl-1,10-	4,6-Diphenyl-8-aminoquinoline	Glycerol	10	282
4,7-Diphenyl-1,10-	4-Phenyl-8-aminoquinoline	$C_6H_5COCH_2CH_2Cl$	40	282
3,4,6-Trimethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	Glycerol	19	271
3,4,7-Trimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_3COCH=CH_2$	31	271
3,4,8-Trimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	271
3,5,6-Tribromo-1,10-	8-Amino-3,5,6-tribromoquinoline	Glycerol	27	316
3,5,6-Trimethyl-1,10-	8-Amino-5,6-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	315
3,5,7-Trimethyl-1,10-	8-Amino-4,6-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	15	317
3,5,8-Trimethyl-1,10-	8-Amino-3,5-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	317
3,6,7-Trimethyl-1,10-	8-Amino-4,5-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	2	317
4,5,7-Trimethyl-1,10-	8-Amino-4,6-dimethylquinoline	$CH_3COCH=CH_2$	1	317
3,5,6,8-Tetrabromo-1,10-	8-Amino-3,5,6-tribromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	4	316
3,4,6,7-Tetramethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	$CH_3COCH=CH_2$	5	271
3,4,6,8-Tetramethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	271
3,4,7,8-Tetramethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_3COCH(CH_3)CH_2OH$	20	271
3,5,6,8-Tetramethyl-1,10-	8-Amino-3,5,6-trimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	22	315

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE IV

COMPOUNDS CONTAINING TWO OR THREE QUINOLINE NUCLEI SEPARATED
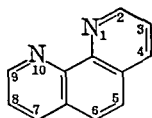BY ONE OR TWO CARBON ATOMS

Product	Reactants	Yield %	References
6,6'-Diquinolylmethane	4,4'-Diaminodiphenylmethane + glycerol	19	202
6,6'-Diquinolyl ketone	4,4'-Diaminodiphenyl ketone + glycerol	—	203
Tri-(6-quinolyl)methane	Pararosaniline + glycerol	—	203
sym-6,6'-Diquinolyl-ethane	sym-4,4'-Diaminodiphenylethane + glycerol	—	204
sym-2,6'-Diquinolyl-ethylene	1-(p-Aminophenyl)-2-(2-quino-lyl)ethylene + glycerol	—	192

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE V

PHENANTHROLINES

A. 1,10-Phenanthrolines

Phenanthroline

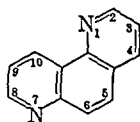|	Reactants		Yield %	References
	Amine	Second Component		
1,10-Phenanthroline	o-Phenylenediamine	Glycerol	45	76
	8-Aminoquinoline	Glycerol	40	71, 78
(5)6-Chloro-1,10-	6-Chloro-8-aminoquinoline	Glycerol	56	79
3-Bromo-1,10-	8-Amino-3-bromoquinoline	Glycerol	20	316
(5)6-Bromo-1,10-	5-Bromo-8-aminoquinoline	Glycerol	40	76
	6-Bromo-8-aminoquinoline	Glycerol	46	79
(5)6-Nitro-1,10-	5-Nitro-8-aminoquinoline	Glycerol	—	76
2-Methyl-1,10-	2-Methyl-8-aminoquinoline	Glycerol	—	183
3-Methyl-1,10-	8-Aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	6	315
4-Methyl-1,10-	8-Amino-4-methylquinoline	Glycerol	15	315
5(6)-Methyl-1,10-	8-Amino-6-methylquinoline	Glycerol	66	79
4-Phenyl-1,10-	8-Aminoquinoline	$C_6H_5COCH_2CH_2Cl$	15	282
	4-Phenyl-8-aminoquinoline	Glycerol	Poor	282
5(6)-Phenyl-1,10-	6-Phenyl-8-aminoquinoline	Glycerol	20	282
3,5-Dibromo-1,10-	8-Amino-6-bromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	1.4	316
3,6-Dibromo-1,10-	8-Amino-3,6-dibromoquinoline	Glycerol	28	316
3,8-Dibromo-1,10-	8-Amino-3-bromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	5	316
5,6-Dibromo-1,10-	8-Amino-5,6-dibromoquinoline	Glycerol	14	316
7-Chloro-3-methyl-1,10-	8-Amino-4-chloroquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	3	315
2-Hydroxy-4-methyl-1,10-	8-Amino-2-hydroxy-4-methylquinoline	Glycerol	20–30	80
2,9-Dimethyl-1,10-	8-Aminoquinaldine	Crotonaldehyde diacetate	7	315
3,4-Dimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	Glycerol	22	271
3,5-Dimethyl-1,10-	8-Amino-6-methylquinoline	$CH_2=C(CH_3)-CH(OCOCH_3)_2$	4	317
3,6-Dimethyl-1,10-	8-Amino-3,6-dimethylquinoline	Glycerol	3	317
3,7-Dimethyl-1,10-	8-Amino-4-methylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	2	315
3,8-Dimethyl-1,10-	8-Amino-3-methylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	315
4,5-Dimethyl-1,10-	8-Amino-4,5-dimethylquinoline	Glycerol	24	317
4,6-Dimethyl-1,10-	8-Amino-4,6-dimethylquinoline	Glycerol	11	317
4,7-Dimethyl-1,10-	8-Amino-4-methylquinoline	$CH_3OCH_2CH_2C(OCH_3)_2CH_3$	7	315
5,6-Dimethyl-1,10-	8-Amino-5,6-dimethylquinoline	Glycerol	9	315
4,6-Diphenyl-1,10-	4,6-Diphenyl-8-aminoquinoline	Glycerol	10	282
4,7-Diphenyl-1,10-	4-Phenyl-8-aminoquinoline	$C_6H_5COCH_2CH_2Cl$	40	282
3,4,6-Trimethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	Glycerol	19	271
3,4,7-Trimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_3COCH=CH_2$	31	271
3,4,8-Trimethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	271
3,5,6-Tribromo-1,10-	8-Amino-3,5,6-tribromoquinoline	Glycerol	27	316
3,5,6-Trimethyl-1,10-	8-Amino-5,6-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	315
3,5,7-Trimethyl-1,10-	8-Amino-4,6-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	15	317
3,5,8-Trimethyl-1,10-	8-Amino-3,5-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	317
3,6,7-Trimethyl-1,10-	8-Amino-4,5-dimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	2	317
4,5,7-Trimethyl-1,10-	8-Amino-4,6-dimethylquinoline	$CH_3COCH=CH_2$	1	317
3,5,6,8-Tetrabromo-1,10-	8-Amino-3,5,6-tribromoquinoline	$CH_2=C(Br)CH(OCOCH_3)_2$	4	316
3,4,6,7-Tetramethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	$CH_3COCH=CH_2$	5	271
3,4,6,8-Tetramethyl-1,10-	3,4,6-Trimethyl-8-aminoquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	9	271
3,4,7,8-Tetramethyl-1,10-	3,4-Dimethyl-8-aminoquinoline	$CH_3COCH(CH_3)CH_2OH$	20	271
3,5,6,8-Tetramethyl-1,10-	8-Amino-3,5,6-trimethylquinoline	$CH_2=C(CH_3)CH(OCOCH_3)_2$	22	315

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE V—*Continued*
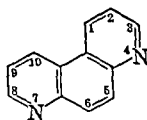
PHENANTHROLINES

B. 1,7-Phenanthrolines

Phenanthroline

	Reactants		Yield	Refer-
	Amine	Second Component	%	ences
1,7-Phenanthroline	*m*-Phenylenediamine	Glycerol	50	36, 43, 70, 71, 72, 183
6-Bromo-1,7-	4-Bromo-*m*-phenylenediamine	Glycerol	30	131
5-Nitro-1,7-	5-Nitro-*m*-phenylenediamine	Glycerol	44	222
2-Hydroxy-1,7-	2-Hydroxy-7-aminoquinoline	Glycerol	50	185
6-Hydroxy-1,7-	5-Amino-8-hydroxyquinoline	Glycerol	40	131
	2,4-Dinitrophenol	Glycerol	10	255
8-Hydroxy-1,7-	2-Hydroxy-5-aminoquinoline	Glycerol	62	185
10-Hydroxy-1,7-	4-Hydroxy-5-aminoquinoline	Glycerol	60	240
2-Methyl-1,7-(together with the linear isomer 2-methyl-1,9-anthra-zoline)	2-Methyl-7-aminoquinoline	Glycerol	—	163
6-Methyl-1,7-	8-Methyl-5-aminoquinoline	Glycerol	—	280
2-Hydroxy-4-methyl-1,7-	2-Hydroxy-4-methyl-7-aminoquinoline	Glycerol	60	185
10-Hydroxy-8-methyl-1,7-	4-Hydroxy-2-methyl-5-aminoquinoline	Glycerol	60	185

C. 4,7-Phenanthrolines

Phenanthroline

	Reactants		Yield	Refer-
	Amine	Second Component	%	ences
4,7-Phenanthroline	*p*-Phenylenediamine	Glycerol	60	36, 70, 71, 72
	p-Nitroaniline	Glycerol	46	73
	6-Aminoquinoline	Glycerol	100	50, 73, 180
1,2,3,4-Tetrahydro-4,7- or the linear isomer 1,2,3,4-tetrahydro-1,6-anthrazoline	1,2,3,4-Tetrahydro-6-aminoquinoline	Glycerol	—	217
6-Bromo-4,7-	8-Bromo-6-aminoquinoline	Glycerol	60	131
1-Hydroxy-4,7-	4-Hydroxy-6-aminoquinoline	Glycerol	Good	186
3-Hydroxy-4,7-	2-Hydroxy-6-aminoquinoline	Glycerol	Quant.	74
1-Hydroxy-3-methyl-4,7-	4-Hydroxy-2-methyl-6-aminoquinoline	Glycerol	88	186
3-Hydroxy-1-methyl-4,7-	2-Hydroxy-4-methyl-6-aminoquinoline	Glycerol	88	50, 186
3-Keto-4-methyl-4,7-	2-Keto-1-methyl-6-aminoquinoline	Glycerol	55	74
1,3-Dimethyl-4,7-	2,4-Dimethyl-6-aminoquinoline	Glycerol	—	143
3,8-Dimethyl-4,7-	*p*-Phenylenediamine	CH₃CH=CHCHO	—	244
5,6-Benzo-4,7-	1,4-Diaminonaphthalene	Glycerol	—	143

D. Other Phenanthrolines

1,8-Phenanthroline	5-Aminoisoquinoline	Glycerol	5	75
5-Methyl-1,6-phenanthroline	2-Methyl-4-aminoquinoline	Glycerol	6	81, 82
5-Methyl-1,6-anthrazoline	5-Methyl-6-acetylaminoquinoline	Glycerol	—	50
2-Hydroxy-4,5,10-tri-methyl-1,6-anthrazoline	2-Hydroxy-4,5,8-trimethyl-6-amino-quinoline	Glycerol	—	50

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE VI

Miscellaneous Quinolines

Product	Reactants		Yield %	References
	Amine	Second Component		
5,6-Trimethylenequinoline	3,4-Trimethyleneaniline	Glycerol	6	94
6,7-Trimethylenequinoline	3,4-Trimethyleneaniline	Glycerol	54	94
7,8-Trimethylenequinoline	2,3-Trimethyleneaniline	Glycerol	60	147
7,12-Diketonaphtho(2,3-h)quinoline	1-Amino-9,10-diketoanthracene	Glycerol	—	43, 60, 61
5,6-Dihydroxy-7,12-diketonaphtho-(2,3-h)quinoline	1-Amino-3,4-dihydroxy-9,10-diketo-anthracene	Glycerol	—	43
8-Amino-9-methyl-7,12-diketonaph-tho(2,3-h)quinoline	1,5-Diamino-2-methyl-9,10-diketo-anthracene	Glycerol	97	63
10-Methyl-11-amino-7,12-diketonaph-tho(3,2-h)quinoline	1,8-Diamino-2-methyl-9,10-diketo-anthracene	Glycerol	—	63
Naphtho(2,3-f)quinoline	2-Aminoanthracene	Glycerol	—	64, 164
7,12-Diketonaphtho(2,3-f)quinoline	2-Amino-9,10-diketoanthracene	Glycerol	—	62
3-Methyl-7,12-diketonaphtho(2,3-f)-quinoline	2-Amino-9,10-diketoanthracene	Paraldehyde	—	60
5,6-Dihydroxy-7,12-diketonaphtho-(2,3-f)quinoline	2-Amino-3,4-dihydroxy-9,10-diketo-anthracene	Glycerol	—	43, 59, 64
6,7-Benz-12-ketonaphtho(2,3-f)-quinoline	2-Amino-9,10-diketoanthracene	Glycerol	—	171
Naphtho(1,2-h)quinoline	1-Aminophenanthrene	Glycerol	—	55
Naphtho(2,1-f)quinoline	2-Aminophenanthrene	Glycerol	90	56
5,6-Dihydronaphtho(1,2-g)quinoline	2-Amino-9,10-dihydrophenanthrene	Glycerol	50	56
Naphtho(1,2-f)quinoline	3-Aminophenanthrene	Glycerol	45	56
Naphtho(2,1-h)quinoline	4-Aminophenanthrene	Glycerol	20	55
Dibenzo(f,h)quinoline	9-Aminophenanthrene	Glycerol	60	54
Pyrenoline	3-Aminopyrene	Glycerol	—	57
11-Indeno(2,1-f)quinoline	2-Aminofluorene	Glycerol	—	65
1,5-Naphthyridine	3-Aminopyridine	Glycerol	28	66, 274, *313*
2-Hydroxy-1,5-naphthyridine	3-Amino-6-hydroxypyridine	Glycerol	15	66, *314*
Thieno(2,3-b)pyridine	2-Aminothiophene	Glycerol	5	67
2-Keto-1,2-dihydro-1-oxa-8-aza-phenanthrene	6-Aminocoumarin	Glycerol	57	68, *300*
9-Methyl-2-keto-1,2-dihydro-1-oxa-8-azaphenanthrene	6-Nitro-7-methylcoumarin	Glycerol	35	68
4,9-Dimethyl-2-keto-1,2-dihydro-1-oxa-8-azaphenanthrene	6-Nitro-4,7-dimethylcoumarin	Glycerol	20	68
9,10-Benz-2-keto-1,2-dihydro-1-oxa-8-azaphenanthrene	6-Nitro-1,2-α-naphthapyrone	Glycerol	30	68
4-Methyl-9,10-benz-2-keto-1,2-dihy-dro-1-oxa-8-azaphenanthrene	6-Nitro-4-methyl-1,2-α-naphtha-pyrone	Glycerol	50	68
Benzofuro(2,3-f)quinoline	3-Aminodibenzofuran	Glycerol	28	*95*, 96, 97
Benzofuro(3,2-g)quinoline	3-Aminodibenzofuran	Glycerol	32	*95*, 96, 97
5-Nitrobenzofuro(2,3-f)quinoline	3-Amino-2-nitrodibenzofuran	Glycerol	24	97
Benzofuro(3,2-f)quinoline	2-Aminodibenzofuran	Glycerol	—	96
Benzofuro(2,3-g)quinoline	2-Aminodibenzofuran	Glycerol	—	96
5-Benzenesulfonamidobenzofuro-(3,2-f)quinoline	2-Amino-3-benzenesulfonamido-dibenzofuran	Glycerol	45	97
12-Xanthono(2,1-b)pyridine	2-Aminoxanthone	Glycerol	—	69
10-Nitro-12-xanthono(2,1-b)pyridine	2,7-Dinitroxanthone	Glycerol	—	69
Pyridino(2',3',4,5)benzothiazole	4-Aminobenzothiazole	Glycerol	30	305
Pyridino(2',3',6,7)benzothiazole	6-Aminobenzothiazole	Glycerol	50	304
2-Methylpyridino(3',2',4,5)benzo-thiazole	5-Amino-2-methylbenzothiazole	Glycerol	—	302

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

TABLE VI—*Continued*

Miscellaneous Quinolines

	Reactants			
Product	Amine	Second Component	Yield %	References
3-Phenyl-3-triazolobenzo(*f*)quinoline	1-Phenyl-5-amino-1-benzotriazole	Glycerol	—	322
2-Phenyl-2-triazolobenzo(*f*)quinoline	2-Phenyl-5-amino-2-benzotriazole	Glycerol	—	322
2-*p*-Tolyl-2-triazolobenzo(*f*)quinoline or 2-*p*-Tolyl-2-triazolobenzo(*g*)quinoline	2-*p*-Tolyl-5-nitro-2-benzotriazole	Glycerol	—	137
Pyridino(3',2',4,5)-benzothiadiazole	5-Aminobenzothiadiazole	Glycerol	—	303
3-Phenyl-3-imidazo(*f*)quinoline	1-Phenyl-5-aminobenzimidazole	Glycerol	—	322
2-Phenyl-3-imidazo(*f*)quinoline	2-Phenyl-5-aminobenzimidazole	Glycerol	35	322
3-*p*-Tolyl-3-imidazo(*f*)quinoline	1-*p*-Tolyl-5-aminobenzimidazole	Glycerol	—	322
1-Phenyl-4-chloro-1-imidazo(*g*)quinoline	1-Phenyl-4-chloro-5-aminobenzimidazole	Glycerol	—	322
1-*p*-Tolyl-4-chloro-1-imidazo(*g*)quinoline	1-*p*-Tolyl-4-chloro-5-aminobenzimidazole	Glycerol	—	322
2-Phenyl-4-bromo-1-imidazo(*g*)quinoline	2-Phenyl-4-bromo-5-aminobenzimidazole	Glycerol	—	322
1-Pyrazolo(3,4-*f*)quinoline	6-Aminoindazole	Glycerol	30	322
9-Chloro-1-pyrazolo(4,3-*g*)quinoline	6-Amino-7-chloroindazole	Glycerol	—	322
Quinolino(8,7-*h*)quinoline	1,5-Diaminonaphthalene	Glycerol	—	194
9,10-Diketodipyridoanthracene	*1,5-Diamino-9,10-anthraquinone*	*Glycerol*	—	61
9,10-Diketodipyridoanthracene	2,6-Diamino-9,10-anthraquinone	Glycerol	—	62
9,10-Diketodipyridoanthracene	2,7-Diamino-9,10-anthraquinone	Glycerol	—	62
Dimethyldipyridoacridine	3,6-Diaminoacridine	CH₃CH=CHCHO	—	244
Dipyrido(2,3-*f*,*h*)quinoline	1,3,5-Triaminobenzene	Glycerol	—	210
Di-6-quinolyl oxide	4,4'-Diaminodiphenyl oxide	Glycerol	—	310

Note: References 116–322 are listed on pp. 94–98. Where one reference is italicized, the yield reported is taken from that reference.

REFERENCES TO TABLES I–VI

116 Rohrmann and Shonle, *J. Am. Chem. Soc.*, **66**, 1643 (1944).

117 Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

118 Farbenfabriken vorm F. Bayer & Co., Brit. pat. 267,457 [*C. A.*, **22**, 1216 (1928)].

119 Strukov, *Org. Chem. Ind.* (*U.S.S.R.*), **4**, 523 (1937) [*C. A.*, **32**, 4987 (1938)].

120 Yanko, Mosher, and Whitmore, *J. Am. Chem. Soc.*, **67**, 664 (1945).

121 v. Braun and Kühlein, *Ber.*, **56**, 1351 (1923).

122 Baldwin and Robinson, *J. Chem. Soc.*, **1934**, 1264.

123 Matejka and Robinson, *J. Chem. Soc.*, **1934**, 1322.

124 McMaster and Bruner, *J. Am. Chem. Soc.*, **57**, 1697 (1935).

125 Vorozhtsov and Troschenko, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 431 (1938) [*C. A.*, **32**, 7908 (1938)].

126 v. Niementowski and Sucharda, *Ber.*, **49**, 12 (1916).

127 Walter, *J. prakt. Chem.*, [2] **49**, 549 (1894).

128 Metzger, *Ber.*, **17**, 186 (1884).

129 Claus and Ammelburg, *J. prakt. Chem.*, [2] **51**, 415 (1895).

130 Claus and Geisler, *J. prakt. Chem.*, [2] **40**, 375 (1889).

131 Haworth and Sykes, *J. Chem. Soc.*, **1944**, 311.

132 Riedel de Haën A.G., Brit. pat. 383,920 [*C. A.*, **27**, 4246 (1933)].

133 Cook, Heilbron, Hey, Lambert, and Spinks, *J. Chem. Soc.*, **1943**, 404.

134 I. G. Farbenindustrie A.G., Brit. pat. 301,947 [*C. A.*, **23**, 4300 (1929)].

135 Barr, *J. Am. Chem. Soc.*, **52**, 2422 (1930).

136 Streitwolf, Fehrle, and Hampe, Ger. pat. 537,365 [*C. A.*, **26**, 998 (1932)].

137 Willgerodt and Dauner, *J. prakt. Chem.*, [2] **60**, 72 (1899).

[138] Berend, *Ber.*, **18**, 376 (1885).

[139] Wikander, *Ber.*, **33**, 646 (1900).

[140] Marckwald, *Ber.*, **23**, 1015 (1890).

[141] Nölting and Frühling, *Ber.*, **21**, 3156 (1888).

[142] Nölting and Kohn, *Ber.*, **19**, 137 (1886).

[143] Marckwald, *Ann.*, **274**, 342, 352 (1893).

[144] Hupe and Schramme, *Z. physiol. Chem.*, **177**, 315 (1928) [*C. A.*, **22**, 4526 (1928)].

[145] Matsumura, *J. Am. Chem. Soc.*, **52**, 3974 (1930).

[146] Fourneau, Tréfouel, Tréfouel, and Benoit, *Ann. inst. Pasteur*, **44**, 719 (1930) [*C. A.*, **26**, 1592 (1932)].

[147] Lindner, Sellner, and Berger, *Monatsh.*, **72**, 330 (1939).

[148] Bamberger and Weitnauer, *Ber.*, **55**, 3376 (1922).

[149] Lindner and Zaunbauer, *Monatsh.*, **72**, 213 (1939).

[150] Kozlov and Golod, *J. Gen. Chem. (U.S.S.R.)*, **6**, 1089 (1936) [*C. A.*, **31**, 1028 (1937)].

[151] Bartow and McCollum, *J. Am. Chem. Soc.*, **26**, 700 (1904).

[152] Lellmann and Lippert, *Ber.*, **24**, 2623 (1891).

[153] Skraup and Brunner, *Monatsh.*, **7**, 139 (1886).

[154] Rodionov and Berkengeĭm, *J. Gen. Chem. (U.S.S.R.)*, **14**, 330 (1944) [*C. A.*, **39**, 4076 (1945)].

[155] v. Braun, Gmelin, and Schultheiss, *Ber.*, **56**, 1338 (1923).

[156] Gilman and Blume, *J. Am. Chem. Soc.*, **65**, 2467 (1943).

[157] Jacobs and Gould, *J. Biol. Chem.*, **120**, 141 (1937).

[158] Glenn and Bailey, *J. Am. Chem. Soc.*, **63**, 637, 639 (1941).

[159] Immerheiser, *Ber.*, **22**, 402 (1889).

[160] Tomita, Uyeo, Inoue, Watanabe, Makino, Mori, Kuwabara, and Kitsutaka, *J. Pharm. Soc. Japan*, **71**, 850 (1951) [*C. A.*, **46**, 3054 (1952)].

[161] Irving, Greene, Peterson, and Capps, *J. Am. Chem. Soc.*, **72**, 4069 (1950).

[162] Baseler Chemische Fabrik, Ger. pat. 102,157 [*Frdl.*, **5**, 172 (1897–1900)].

[163] v. Braun, Heider, and Wyczatkowska, *Ber.*, **51**, 1215 (1918).

[164] Graebe, *Ber.*, **17**, 170 (1884).

[165] Skraup, *Monatsh.*, **6**, 760 (1885).

[166] Maschmann, *Ber.*, **59**, 2825 (1926).

[167] Iwamiya, *J. Pharm. Soc. Japan*, **49**, 792 (1929) [*C. A.*, **24**, 119 (1930)].

[168] Grimaux, *Compt. rend.*, **121**, 749 (1895).

[169] Späth and Brunner, *Ber.*, **57**, 1243 (1924).

[170] Lempert and Robinson, *J. Chem. Soc.*, **1934**, 1419.

[171] Bally, *Ber.*, **38**, 194 (1905).

[172] Fränkel and Grauer, *Ber.*, **46**, 2551 (1913).

[173] Freyss and Paira, *Bull. soc. ind. Mulhouse*, **72**, 239 (1902) [*Brit. Chem. Abstracts*, **84**, 198 (1903)].

[174] King and Sherred, *J. Chem. Soc.*, **1942**, 415.

[175] La Coste, *Ber.*, **16**, 669 (1883).

[176] Barbier, *Bull. soc. chim. France*, [4] **27**, 427 (1920).

[177] La Coste, *Ber.*, **15**, 557 (1882).

[178] Fischer and Fränkel, *Ber.*, **19**, 749 (1886).

[179] Lellmann and Alt, *Ann.*, **237**, 307 (1887).

[180] Kaufmann and Radosevic, *Ber.*, **42**, 2612 (1909).

[181] Cook, Heilbron, and Steger, *J. Chem. Soc.*, **1943**, 413.

[182] Tortelli, *Gazz. chim. ital.*, **16**, 366 (1887).

[183] Gerdeissen, *Ber.*, **22**, 244 (1889).

[184] Sveinbjornsson, Bradlow, Oae, and Vanderwerf, *J. Org. Chem.*, **16**, 1450 (1951).

[185] Kermack and Webster, *J. Chem. Soc.*, **1942**, 213.

[186] Kermack and Weatherhead, *J. Chem. Soc.*, **1940**, 1164.

[187] La Coste, *Ber.*, **18**, 2940 (1885).

[188] Koenigs and Nef, *Ber.*, **20**, 622 (1887).

[189] v. Miller and Kinkelin, *Ber.*, **18**, 1900 (1885).

[190] Claus and Tornier, *Ber.*, **20**, 2872 (1887).

[191] v. Miller and Kinkelin, *Ber.*, **20**, 1919 (1887).

[192] Bulach, *Ber.*, **22**, 285 (1889).

[193] Claus and Vis, *J. prakt. Chem.*, [2] **38**, 387 (1888).

[194] Finger and Spitz, *J. prakt. Chem.*, [2] **79**, 445 (1909).

[195] Claus and Schöller, *J. prakt. Chem.*, [2] **48**, 140 (1893).

[196] Fourneau, Tréfouel, Tréfouel, and Wancolle, *Bull. soc. chim. France*, [4] **47**, 738 (1930).

[197] Claus and Howitz, *J. prakt. Chem.*, [2] **48**, 151 (1893).

[198] Claus and Stegelitz, *Ber.*, **17**, 2380 (1884).

[199] Fischer, *Monatsh.*, **6**, 546 (1885).

[200] v. Niementowski and Seifert, *Ber.*, **38**, 762 (1905).

[201] Kaslow and Hayek, *J. Am. Chem. Soc.*, **73**, 4986 (1951).

[202] Borsche and Kienitz, *Ber.*, **43**, 2333 (1910).

[203] Nölting and Schwartz, *Ber.*, **24**, 1606 (1891).

[204] Comey, *Ber.*, **23**, 1115 (1890).

[205] v. Jakubowski and v. Niementowski, *Ber.*, **42**, 634 (1909).

[206] Bratz and v. Niementowski, *Ber.*, **52**, 193 (1919).

[207] Doebner and v. Miller, *Ber.*, **14**, 2812 (1881).

[208] Wallach and Wüsten, *Ber.*, **16**, 2007 (1883).

[209] Heou-Feo, *Bull. soc. chim. France*, [5] **2**, 90 (1935).

[210] Pictet and Barbier, *Bull. soc. chim. France*, [3] **13**, 26, 28 (1895).

[211] Dodge, U. S. pat. 2,211,538 [*C. A.*, **35**, 1069 (1941)].

[212] Koenigs and Jaeglé, *Ber.*, **28**, 1046 (1895).

[213] Ukai, *J. Pharm. Soc. Japan*, **543**, 873 (1927) [*C. A.*, **22**, 785 (1928)].

[214] Schlosser and Skraup, *Monatsh.*, **2**, 518 (1881).

[215] Reed, *J. prakt. Chem.*, [2] **32**, 630 (1884); [2] **35**, 298 (1887).

[216] Johnson and Mathews, *J. Am. Chem. Soc.*, **66**, 210 (1944).

[217] Lindner, *Monatsh.*, **42**, 421 (1921).

[218] Ghosh, Banerjee, and Lasker, *J. Indian Chem. Soc.*, **21**, 354 (1944) [*C. A.*, **39**, 2998 (1945)].

[219] Kermack, Muir, and Wight, *J. Chem. Soc.*, **1935**, 1143.

[220] Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J. Chem. Soc.*, **1943**, 401.

[221] Miklaszewski and v. Niementowski, *Ber.*, **34**, 2971 (1901).

[222] Korczynski and Brydowna, *Bull. soc. chim. France*, [4] **37**, 1483 (1925).

[223] Bogert and Meyer, *J. Am. Chem. Soc.*, **44**, 1572 (1922).

[224] v. Niementowski, *Ber.*, **32**, 1490 (1899).

[225] Ueda, *J. Pharm. Soc. Japan*, **57**, 185 (1937) [*C. A.*, **33**, 608 (1939)].

[226] Isiwara, Jap. pat. 94,165 [*C. A.*, **27**, 2697 (1933)].

[227] Claus and Posselt, *J. prakt. Chem.*, [2] **41**, 32 (1890).

[228] Capps and Hamilton, *J. Am. Chem. Soc.*, **60**, 2104 (1938).

[229] Decker, *J. prakt. Chem.*, [2] **63**, 573 (1901).

[230] Buu-Hoï and Guettier, *Compt. rend.*, **222**, 665 (1946).

[231] Bose, *J. Indian Chem. Soc.*, **22**, 169 (1945) [*C. A.*, **40**, 5437 (1946)].

[232] Giral and Calderón, *Ciencia (Mexico)*, **6**, 17 (1945) [*C. A.*, **40**, 5052 (1946)].

[233] Étienne, *Compt. rend.*, **219**, 397 (1944).

[234] Kochańska and Bobrański, *Ber.*, **69**, 1807 (1936).

[235] Claus and Stiebel, *Ber.*, **20**, 3095 (1887).

[236] Lellmann and Lange, *Ber.*, **20**, 1446 (1887).

[237] Gilman and Lindblad, *J. Am. Chem. Soc.*, **68**, 982 (1946).

[238] Linsker and Evans, *J. Am. Chem. Soc.*, **68**, 874 (1946).

[239] Morgan and Cretcher, *J. Am. Chem. Soc.*, **68**, 781 (1946).

[240] Kermack and Tebrich, *J. Chem. Soc.*, **1945**, 375.

[241] Chelintsev and Zakotin, *J. Gen. Chem. (U.S.S.R.)*, **11**, 729 (1941) [*C. A.*, **36**, 477 (1942)].

[242] Coles and Hamilton, *J. Am. Chem. Soc.*, **68**, 1595 (1946).

[243] Snyder and Easton, *J. Am. Chem. Soc.*, **68**, 1549 (1946).

[244] Kunz, Kochendoerfer, and Köberle, Ger. pat. 567,273 [*C. A.*, **27**, 1362 (1933)].

[245] Berend, *Ber.*, **17**, 1489 (1884).

[246] Tomisek, Graham, Griffith, Pease, and Christensen, *J. Am. Chem. Soc.*, **68**, 1587 (1946).

[247] Gilman, Benkeser, Gainer, Lindblad, Marshall, Massie, Myers, and Tolman, *J. Am. Chem. Soc.*, **68**, 1577 (1946).

[248] Morgan and Tipson, *J. Am. Chem. Soc.*, **68**, 1569 (1946).

[249] Lauer, Arnold, Tiffany, and Wilson, *J. Am. Chem. Soc.*, **68**, 1548 (1946).

[250] Lauer, Rondestvedt, Arnold, Drake, Van Hook, and Tinker, *J. Am. Chem. Soc.*, **68**, 1546 (1946).

[251] Drake, Anspon, Draper, Haywood, Van Hook, Melamed, Peck, Sterling, Walton, and Whiton, *J. Am. Chem. Soc.*, **68**, 1536 (1946).

[252] Baker, Albisetti, Dodson, Lappin, and Riegel, *J. Am. Chem. Soc.*, **68**, 1532 (1946).

[253] Borsche and Groth, *Ann.*, **549**, 238 (1941).

[254] Carmack, Kissinger, and Von, *J. Am. Chem. Soc.*, **68**, 1551 (1946).

[255] Ghosh, Roy, and Banerjee, *J. Indian Chem. Soc.*, **22**, 219 (1945) [*C. A.*, **40**, 5746 (1946)].

[256] Campbell, Kerwin, LaForge, and Campbell, *J. Am. Chem. Soc.*, **68**, 1844 (1946).

[257] LeConte, *Mitchell Sci. Soc.*, **51**, 249 (1935) [*C. A.*, **30**, 4497 (1936)].

[258] Seibert, Norton, Benson, and Bergstrom, *J. Am. Chem. Soc.*, **68**, 2721 (1946).

[259] Capps, *J. Am. Chem. Soc.*, **69**, 179 (1947).

[260] Bachman and Wetzel, *J. Org. Chem.*, **11**, 454 (1946).

[261] Berend, *Ber.*, **17**, 2716 (1884).

[262] Ewins, *J. Chem. Soc.*, **103**, 97 (1913).

[263] Pouterman and Girardet, *Experienta*, **3**, 28 (1947) [*C. A.*, **41**, 4493 (1947)].

[264] Pouterman and Girardet, *Helv. Chim. Acta*, **30**, 107 (1947).

[265] Mailhe, *Compt. rend.*, **173**, 160 (1921).

[266] Curd, Graham, Richardson, and Rose, *J. Chem. Soc.*, **1947**, 1613.

[267] Kermack and Wight, *J. Chem. Soc.*, **1935**, 1421.

[268] Magidson, Delektorskaya, and Lipovich, *Arch. Pharm.*, **272**, 74 (1934) [*C. A.*, **28**, 3477 (1934)].

[269] Saunders, Smith, and Capps, *J. Am. Chem. Soc.*, **73**, 5910 (1951).

[270] Weizmann and Bograchov, *J. Am. Chem. Soc.*, **69**, 1222 (1947).

[271] Case, *J. Am. Chem. Soc.*, **71**, 1828 (1949).

[272] Chakravarti and Venkatasubban, *J. Annamalai Univ.*, **2**, 227 (1933) [*C. A.*, **28**, 2008 (1934)].

[273] Gattermann and Kaiser, *Ber.*, **18**, 2602 (1885).

[274] Bobrański and Sucharda, *Ber.*, **60**, 1081 (1927).

[275] Ukai, Hashimoto, and Higashi, *J. Pharm. Soc. Japan*, **48**, 371 (1928) [*C. A.*, **22**, 3166 (1928)].

[276] Wheeler and LeConte, *J. Am. Chem. Soc.*, **70**, 386 (1948).

[277] Alt, *Ann.*, **252**, 318 (1889).

[278] Linsker and Evans, *J. Am. Chem. Soc.*, **68**, 149 (1946).

[279] Gerd and Kochendoefer, Ger. pat. 613,066 [*C. A.*, **29**, 5163 (1935)].

[280] Nölting and Trautmann, *Ber.*, **23**, 3654 (1890).

[281] Bogert and Fisher, *J. Am. Chem. Soc.*, **34**, 1569 (1912).

[282] Case, *J. Org. Chem.*, **16**, 1541 (1951).

[283] Clemo and Legg, *J. Chem. Soc.*, **1947**, 539.

[284] Haskelberg, *J. Org. Chem.*, **12**, 434 (1947).

[285] Cornforth and Cornforth, *J. Chem. Soc.*, **1948**, 93.

[286] Hoffmann, *Bull. soc. chim. France*, **1947**, 969.

[287] Lellmann and Ziemssen, *Ber.*, **24**, 2116 (1891).

[288] Wieland and Horner, *Ann.*, **536**, 89 (1938).

[289] Edinger and Bühler, *Ber.*, **42**, 4313 (1909).

[290] Jones, Soper, Behrens, and Corse, *J. Am. Chem. Soc.*, **70**, 2843 (1948).

[221] McCasland, *J. Am. Chem. Soc.*, **68**, 533 (1946).

[222] Fischer and Willmack, *Ber.*, **17**, 440 (1884).

[223] Herzfeld, *Ber.*, **17**, 903 (1884).

[224] Rajagopalan, *Proc. Indian Acad. Sci.*, **13A**, 566 (1941) [*C. A.*, **35**, 7965 (1941)].

[225] I. G. Farbenindustrie A.G., Swiss pat. 127,178 [*C. A.*, **23**, 1218 (1929)].

[226] I. G. Farbenindustrie A.G., Brit. pat. 307,727 [*C. A.*, **24**, 128 (1930)].

[227] Radionov and Antik, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 423 (1941) [*C. A.*, **37**, 2009 (1943)].

[228] Huisgen, *Ann.*, **559**, 174 (1948).

[229] Happ, *Ber.*, **17**, 191 (1884).

[300] Petrow and Rewald, *J. Chem. Soc.*, **1949**, 769.

[301] Waley, *J. Chem. Soc.*, **1948**, 2008.

[302] Fries and Wolter, *Ann.*, **527**, 60 (1936).

[303] Fries and Reitz, *Ann.*, **527**, 38 (1936).

[304] Boggust and Cocker, *J. Chem. Soc.*, **1949**, 355.

[305] Erlenmeyer and Ueberwasser, *Helv. Chim. Acta*, **23**, 328 (1940).

[305] Niederl, U. S. pat. 2,483,838 [*C. A.*, **44**, 2035 (1950)].

[337] Taylor, *J. Chem. Soc.*, **1951**, 1150.

[308] Bendz, Culvenor, Goldsworthy, Kirby, and Robinson, *J. Chem. Soc.*, **1950**, 1130.

[309] Diaz de Arce, Greene, and Capps, *J. Am. Chem. Soc.*, **72**, 2971 (1950).

[310] Tomita, Fujita, Yoshida, and Tokuyama, *J. Pharm. Soc. Japan*, **69**, 401 (1949) [*C. A.*, **44**, 1983 (1950)].

[311] Alamela and Dey, *Proc. Natl. Inst. Sci. India*, **7**, 215 (1941) [*C. A.*, **43**, 1422 (1949)].

[312] Campbell, LaForge, and Campbell, *J. Org. Chem.*, **14**, 346 (1949).

[313] Hauser and Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).

[314] Petrow and Sturgeon, *J. Chem. Soc.*, **1949**, 1157.

[315] Case, *J. Am. Chem. Soc.*, **70**, 3994 (1948).

[316] Case, *J. Org. Chem.*, **16**, 941 (1951).

[317] Case, *J. Am. Chem. Soc.*, **71**, 821 (1949).

[318] Lott, Yale, Sheehan, and Bernstein, *J. Am. Chem. Soc.*, **70**, 3621 (1948).

[319] Robinson and Stephen, *Nature*, **162**, 177 (1948) [*C. A.*, **43**, 3421 (1949)].

[320] Gilman and Gainer, *J. Am. Chem. Soc.*, **71**, 1747 (1949).

[321] Baker, Tinsley, Butler, and Riegel, *J. Am. Chem. Soc.*, **72**, 393 (1950).

[322] Fries, *Ann.*, **454**, 121 (1927).

CHAPTER 3

CARBON-CARBON ALKYLATIONS WITH AMINES AND AMMONIUM SALTS

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CONTENTS

INTRODUCTION

This chapter is a review of those reactions of compounds containing labile amino groups in which a carbon-carbon bond is formed by amine replacement, as, for example, in the alkylation of diethyl malonate by 1-dimethylamino-3-butanone.

$$CH_3COCH_2CH_2N(CH_3)_2 + CH_2(CO_2C_2H_5)_2 \rightarrow$$

$$CH_3COCH_2CH_2CH(CO_2C_2H_5)_2 + (CH_3)_2NH$$
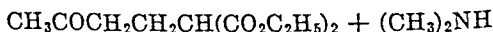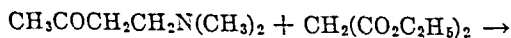
In the most general terms, these alkylation reactions may be written

$$ZCH_2NR_1R_2 + HY \rightarrow ZCH_2Y + HNR_1R_2$$

or

$$ZCH_2\overset{+}{N}R_1R_2R_3X^- + MY \rightarrow ZCH_2Y + NR_1R_2R_3 + MX$$

where

$$Z = R-\overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{C}}-CH- , \quad \quad , \quad \quad , \quad \quad , \text{ etc.;}$$
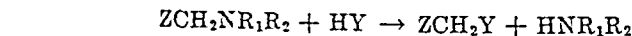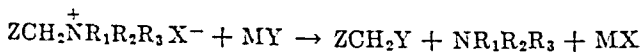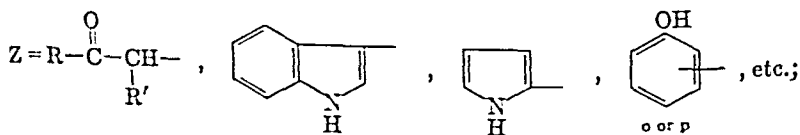
HY = hydrogen cyanide, active methyl and methylene compounds; and
MY = alkali cyanides, sodio derivatives of active methyl or methylene compounds, Grignard reagents, or organolithium compounds.

Attention has been given primarily to reactions of amines that can be prepared by the Mannich reaction [1] (Mannich bases), but, for com-

[1] Blicke in Adams, *Organic Reactions*, Vol. I, p. 303, John Wiley & Sons, 1942.

parison, analogous reactions of simpler quaternary ammonium salts have been included in the discussion and tables. A number of reactions which are closely related to these simple alkylations but follow a somewhat different pattern are discussed in the Related Reactions section and are not included in the tables.

SCOPE AND LIMITATIONS

General Considerations

The most important groups of compounds capable of engaging in carbon-carbon alkylations by amine replacement are:

(*a*) Simple quaternary ammonium salts containing benzyl and methyl radicals. The general formulation of carbon-carbon alkylation with such salts corresponds to the third equation on p. 102

(*b*) Tertiary amines that can be prepared from ketones, phenols, heterocyclic compounds, and nitro compounds by the Mannich reaction.[1]

$$R{-}\underset{\underset{R'}{\displaystyle |}}{\overset{\overset{O}{\displaystyle \|}}{C}}{-}\overset{H}{\underset{}{C}}{-}H + CH_2O + HNR_2 \cdot HCl \rightarrow$$

$$R{-}\overset{\overset{O}{\displaystyle \|}}{C}{-}\underset{\underset{R'}{\displaystyle |}}{\overset{H}{C}}{-}CH_2NR_2 \cdot HCl + H_2O$$

$$\text{phenol (OH)} + CH_2O + HNR_2 \rightarrow \text{phenol (OH)(CH}_2\text{NR}_2) + H_2O$$

$$\text{indole} + CH_2O + HNR_2 \rightarrow \text{indole (CH}_2\text{NR}_2) + H_2O$$

$$CH_3CH_2CH_2NO_2 + CH_2O + HNR_2 \rightarrow CH_3CH_2CH(NO_2)CH_2NR_2 + H_2O$$
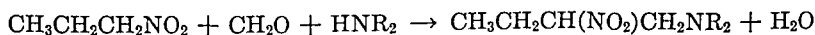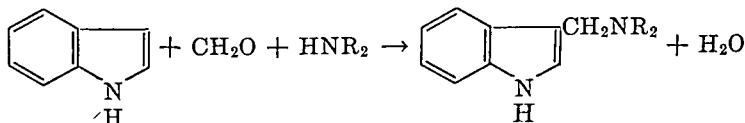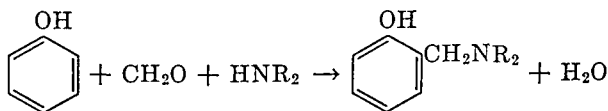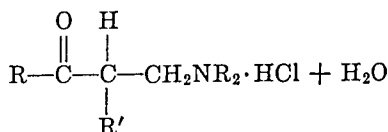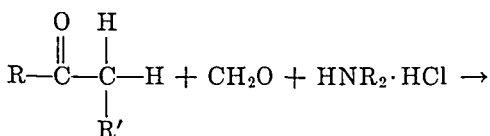
The general form of the reactions of carbon-carbon alkylations by amine replacement undergone by these Mannich bases is shown in the second equation on p. 102.

(c) Quaternary salts of Mannich bases, which can be formed by reaction of the tertiary amines with alkyl halides or dimethyl sulfate.

$$ZCH_2NR_2 + R'X \rightarrow ZCH_2\overset{+}{N}R_2R'X^-$$
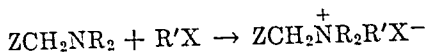
The general form of the reactions undergone by these salts is shown in the third equation on p. 102.

Structural Considerations

Structure of the Alkylating Radical. The ability to form a conjugated unsaturated system by amine elimination seems to be the main structural requirement for facile carbon-carbon alkylations by amine replacement with tertiary amines (see p. 126). The structural features required for amine elimination are indicated in formulas I and II. An enolizable hydrogen atom must be so located that when it and the dialkylamino

$$\underset{\text{I}}{A{=}C{-}\overset{\overset{\displaystyle H}{|}}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}NR_2} \rightarrow A{=}C{-}C{=}\overset{|}{C} + HNR_2$$

$$\underset{\text{II}}{HA{=}C{-}\overset{|}{\underset{|}{C}}{-}NR_2} \rightarrow A{=}C{-}C{=}\overset{|}{C} + HNR_2$$
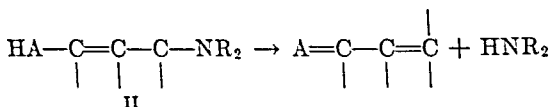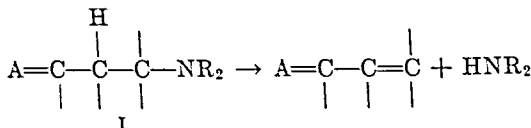
group are removed from the molecule a conjugated unsaturated system can be established by electron transfer.

The structural characteristics necessary for *easy* carbon-carbon alkylations with quaternary ammonium salts are similar. A number of quaternary salts that cannot undergo amine elimination can be used as alkylating agents, although in general the reactions are much slower than those of quaternary salts which can suffer amine elimination. Where amine elimination is not possible, the structural requirement of the alkylating radical appears to be either the presence of an allylic system, as in benzyl, 1-methylskatyl (III), and furfuryl radicals, or freedom from steric hindrance to rearward attack, as in the methyl radical.

III
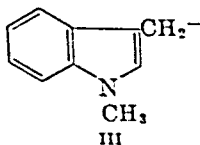
Structure of the Amino Group Replaced. The structure of the amino group replaced in carbon-carbon alkylations of this type is of some importance in the economic and operational aspects of these reactions. The presence of certain amino groups that could undergo alkylation by the alkylating radical, such as derivatives of aniline, is probably undesirable in some of these reactions.

Structure of the Substance To Be Alkylated. Only those substances that can easily form anions can be alkylated by Mannich bases or quaternary salts. Active methylene compounds and their sodio derivatives, hydrogen cyanide and its salts, and organometallic compounds such as Grignard reagents and alkyl- or aryl-lithium compounds constitute the principal members of this class of substances.

The carbon-carbon alkylations with amines and ammonium salts to be considered in detail are the following.

(a) Replacement of amino groups by cyanide
(b) Alkylation of active methyl and methylene compounds
    1. Alkylation of aliphatic nitro compounds
    2. Alkylation of ketones and β-keto esters
    3. Alkylation of esters
    4. An alkylation of indole
(c) Amine replacement reactions of quaternary salts with organometallic compounds.

Replacement of Amino Groups by Cyanide

Quaternary Ammonium Salts and Alkali Cyanides. Quaternary ammonium cyanides are difficult to prepare, but mixtures of certain quaternary ammonium salts with alkali cyanides decompose when strongly heated in a manner expected of quaternary ammonium cyanides. The reactions are analogous to those of quaternary ammonium halides in that benzyl and methyl groups are cleaved from the quaternary nitrogen atom and couple with the anion of the salt. In at least one reaction, however, olefin formation, similar to that found in the Hofmann exhaustive methylation, occurs more readily than does simple amine replacement.[2]

When tetramethylammonium cyanide is heated, acetonitrile, methylcarbylamine, and trimethylamine are formed.[3] Acetonitrile and methylethylaniline are formed when a mixture of potassium cyanide and dimethylethylanilinium iodide is distilled to dryness.[4]

[2] Snyder and Brewster, *J. Am. Chem. Soc.*, **71**, 291 (1949).

[3] Thompson, *Ber.*, **16**, 2338 (1883).

[4] von Meyer and Schwabe, *Abhandl. math.-phys. Klasse sächs. Ges. Wiss.*, **31**, 179 (1908) [*Chem. Zentr.*, **80**, II, 1800 (1909); *C. A.*, **5**, 887 (1911)].

Although benzyldimethylanilinium halides do not react appreciably
with sodium cyanide in boiling water,[5] benzyl cyanide is formed when an
aqueous solution of the two salts is distilled to dryness.[4] Similarly, the
methiodide of 1-dimethylaminomethyl-2-methoxynaphthalene (IV,
R = CH₃) reacts with sodium cyanide to form 2-methoxy-1-naphthyl-
acetonitrile (V, R = CH₃) only when an aqueous solution of the two
salts is evaporated to dryness and distilled in vacuum at temperatures
above 150°.[6] On the other hand, when a mixture of sodium cyanide and
N,N,N-trimethyl-α-phenylethylammonium iodide (VI) was similarly

$$CH_2N(CH_3)_2 \qquad\qquad CH_2CN$$

$$OR \qquad\qquad\qquad OR$$

IV   V
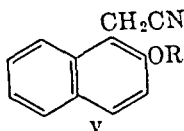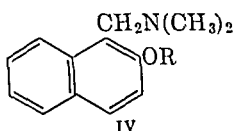
treated, styrene was formed and no hydratroponitrile could be detected
in the reaction products.[2]

$$[C_6H_5CHN(CH_3)_3]^+ I^-$$
$$|$$
$$CH_3$$

VI
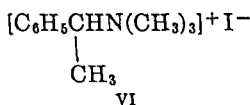
Although none of the reactions described above is of preparative
interest, since the corresponding methyl and benzyl halides are readily
available, the analogous reactions of the quaternary salts of Mannich
bases derived from indole are useful in the preparation of indoleaceto-
nitriles. The methiodide of gramine [6a,b,c] (3-dimethylaminomethyl-
indole, VIIa) reacts with potassium silver cyanide in boiling water to
form indole-3-acetonitrile (VIII), isolated as the acid in 46% yield.[6c,7]
The methosulfate of gramine reacts readily with potassium cyanide in
aqueous ethanol to form the same nitrile (VIII) (isolated as the acid in
50% yield from gramine).[8,8a] The quaternary salt of gramine is formed

$$CH_2NR_2 \qquad\qquad CH_2CN$$

$$N \qquad\qquad\qquad N$$
$$H \qquad\qquad\qquad H$$
VII   VIII
VIIa Gramine; R = CH₃
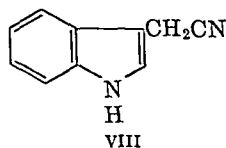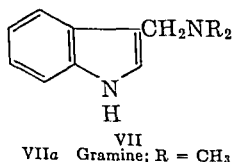
[5] Snyder and Speck, J. Am. Chem. Soc., **61**, 668 (1939).
[6] Snyder and Brewster, J. Am. Chem. Soc., **71**, 1058 (1949).
[6a] Schramm, J. Am. Chem. Soc., **73**, 2961 (1951).
[6b] Schöpf and Thesing, Angew. Chem., **63**, 377 (1951).
[6c] Geissman and Armen, J. Am. Chem. Soc., **74**, 3916 (1952).
[7] Snyder, Smith, and Stewart, J. Am. Chem. Soc., **66**, 200 (1944).
[8] Heidelberger, J. Biol. Chem., **179**, 139 (1949).
[8a] Thesing and Schülde, Chem. Ber., **85**, 324 (1952).

in situ by the addition of dimethyl sulfate to the solution of gramine and potassium cyanide. The methiodide of 1-methylgramine (IX) reacts with hot aqueous sodium cyanide to give mainly the expected product, 1-methyl-3-indoleacetonitrile (X, 60–64%), together with smaller amounts of 1,3-dimethyl-2-cyanoindole (XI, 4%),[9] apparently by an allylic rearrangement during the alkylation process. The Mannich bases of N-methyl- and N-phenyl-pyrrole yield the normal products only.[9a]
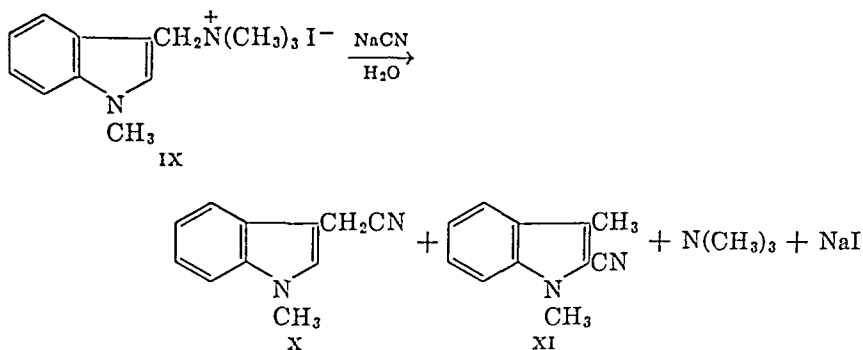
In a similar fashion, furfuryltrimethylammonium iodide (XII, R = H) yields a mixture of furfuryl cyanide (XIII, R = H, 27%) and 2-cyano-5-methylfuran (XIV, 5%), and 5-methylfurfuryltrimethylammonium iodide (XII, R = CH₃) gives 5-methylfurfuryl cyanide (XIII, R = CH₃) in 37% yield.[10]

The methiodide of β-dimethylaminopivalophenone (XV) reacts with sodium cyanide when an aqueous solution of the two salts is distilled to form β-dimethylaminopivalophenone (XV) and, presumably, acetonitrile.[11]
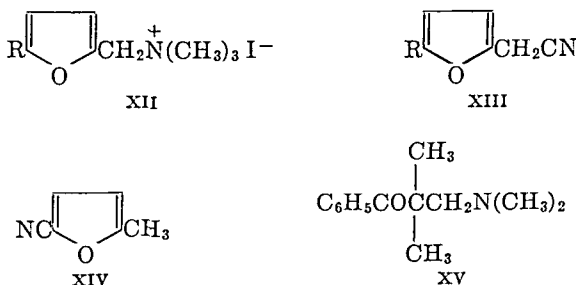
[9] Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 1703, 1857 (1948).
[9a] Herz and Rogers, *J. Am. Chem. Soc.*, **73**, 4921 (1951).
[10] Eliel and Peckham, *J. Am. Chem. Soc.*, **72**, 1209 (1950).
[11] Snyder and Brewster, *J. Am. Chem. Soc.*, **71**, 1061 (1949).

Tertiary Amines and Hydrogen Cyanide. Tertiary amines capable of eliminating a secondary amine to form a conjugated unsaturated structure can react with hydrogen cyanide to form nitriles by amine replacement.

3-Dialkylaminomethylindoles (VII) react with hydrogen cyanide in benzene solution at 150° to form indole-3-acetonitrile (VIII);[12] under similar conditions 1-dimethylaminomethyl-2-hydroxynaphthalene (IV, R = H) reacts with hydrogen cyanide to form 2-hydroxy-1-naphthaleneacetonitrile (V, R = H).[12] No information on the yields obtainable by this process is available.

Hydrochlorides of a number of ketonic Mannich bases have been found to react readily with alkali metal cyanides in hot water to form γ-ketonitriles in good yield.[13] No successful application of this reaction to wholly aliphatic ketonic Mannich bases has been reported; the hydrochloride of 2-dimethylaminomethylcyclohexanone (XVI) formed only a resin or oil when heated with potassium cyanide in aqueous solution.[13] Ketonic Mannich base hydrochlorides of structure XVII have been found to react satisfactorily with aqueous potassium cyanide when R is furyl, benzofuryl, thienyl, phenyl, 3-hydroxy- and 3-methoxyphenyl, 4-methyl-, 4-chloro-, 4-bromo-, 4-hydroxy-, and 4-methoxy-

$$\underset{\text{XVI}}{\overset{\displaystyle =O}{\underset{CH_2N(CH_3)_2}{\bigcirc}}}$$

$$\underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{RCOCCH_2N(CH_3)_2 \cdot HCl}} + KCN \rightarrow \underset{\underset{R_2}{|}}{\overset{\overset{R_1}{|}}{RCOCCH_2CN}} + HN(CH_3)_2 + KCl$$

XVII $R_1 = R_2 = H$

phenyl; 3,4-dimethoxyphenyl, α- or β-naphthyl. The hydrochloride of β-dimethylamino-3-nitropropiophenone formed resins when heated with aqueous potassium cyanide.[13]

Substituents on the carbon atom adjacent to the carbonyl group appear to interfere with the reaction with cyanides. The hydrochloride of α-dimethylaminomethylpropiophenone (XVII, R_1 = H, R_2 = CH$_3$) formed a resin or oil,[13] and the hydrochloride of dimethylaminopivalophenone (XVII, R_1 = R_2 = CH$_3$) underwent a reverse Mannich reaction to form isobutyrophenone.[11]

[12] Salzer and Andersag, U. S. pat. 2,315,661 [C. A., 37, 5418 (1943)]; U. S. PB 706, Dept. of Commerce, Washington, D. C.

[13] Knott, J. Chem. Soc., 1947, 1190.

It has been reported that the salts of Mannich bases made from piperidine or morpholine do not react under conditions [13] suitable for dimethylamine derivatives. It seems likely that this is at least partly due to the fact that the amines being replaced are less volatile than the solvent.

Tertiary Amines and Alkali Cyanides. The Mannich bases of phenols and indoles react with sodium cyanide in hot aqueous ethanol to form sodium salts of aryl- and indole-acetic acids.[12] Little information on yields and the by-products formed is available, though it is reported that condensation products are formed from phenolic Mannich bases. This is not surprising since phenolic Mannich bases readily undergo self-alkylation in weakly alkaline solution to form diarylmethanes.[14]

$$2ZCH_2NR_1R_2 + H_2O \rightarrow ZCH_2Z + CH_2O + 2HNR_1R_2$$

In the reaction of 1-dimethylaminomethyl-2-naphthol with sodium cyanide it was found that 2-hydroxy-1-naphthaleneacetic acid (XVIII) could be isolated in 47% yield, and the diarylmethane (XIX) was formed in at least 20% yield.[15] It seems likely that diarylmethane formation would be a major side reaction in any similar application of this method and that phenolic Mannich bases containing unsubstituted *ortho* or *para* positions would form appreciable amounts of polymeric materials, as has

XVIII (47%)

XIX (20%)

been observed in the reaction of 6-dimethylaminomethylguaiacol with sodium cyanide.[15a]

Several 3-dialkylaminomethylindoles (VII) have been subjected to reaction with cyanide, but information as to yields is available only for dimethylaminomethylindole (gramine, VIIa) which in hot aqueous

[14] Auwers and Dombrowski, *Ann.*, **344**, 280 (1906).

[15] J. Brewster, doctoral thesis, University of Illinois, Urbana, Ill., 1948.

[15a] Eliel, *J. Am. Chem. Soc.*, **73**, 43 (1951).

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XVI

$$\text{RCOCCH}_2\text{N(CH}_3)_2 \cdot \text{HCl} + \text{KCN} \rightarrow \text{RCOCCH}_2\text{CN} + \text{HN(CH}_3)_2 + \text{KCl}$$

XVII   R₁ = R₂ = H

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[13] Knott, *J. Chem. Soc.*, **1947**, 1190.

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[14] Auwers and Dombrowski, *Ann.*, **344**, 280 (1906).
[15] J. Brewster, doctoral thesis, University of Illinois, Urbana, Ill., 1948.
[15a] Eliel, *J. Am. Chem. Soc.*, **73**, 43 (1951).

ethanol gave a 69% yield of 3-indoleacetic acid (XX) and a 20% yield of 3-indoleacetamide with little or no diindolylmethane.[16] Indoleacetamide may be hydrolyzed to the acid in good yield.[16]

XX   XXI
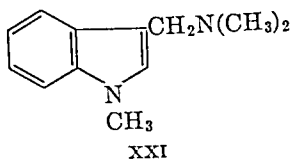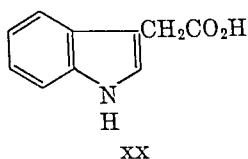
Compounds that cannot suffer amine elimination, such as 1-methylgramine [17] (XXI) and 1-dimethylaminomethyl-2-methoxynaphthalene [6] (IV, R = CH₃) fail to react with sodium cyanide under the above conditions.

Alkylation of Active Methyl and Methylene Compounds

Alkylation of Aliphatic Nitro Compounds. Alkylations of aliphatic nitro compounds by p-nitrobenzyltrimethylammonium iodide and Mannich bases of indole, of ketones, and of aliphatic nitro compounds have been reported.

Gramine (VIIa) reacts smoothly with 1- or 2-nitropropane in the presence of sodium hydroxide to give good yields of monoalkylated nitro compound; much lower yields are obtained with nitroethane.[18]   Only

VIIa
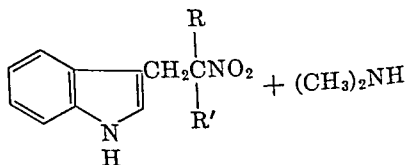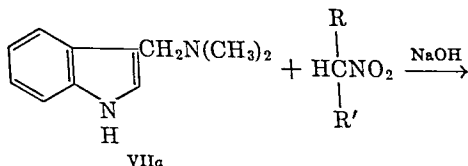
diskatylnitromethane (XXII) was obtained by alkylation of nitromethane under these conditions.[18]

[16] Snyder and Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).
[17] Snyder and Eliel, *J. Am. Chem. Soc.*, **71**, 663 (1949).
[18] Snyder and Katz, *J. Am. Chem. Soc.*, **69**, 3140 (1947).

$$2 \underset{\text{VII}a}{\text{(indole ring)}} \text{—CH}_2\text{N(CH}_3)_2 + \text{CH}_3\text{NO}_2 \xrightarrow{\text{NaOH}}$$

$$\left[\underset{\text{XXII}}{\text{(indole ring)}} \text{—CH}_2 \right]_2 \text{CHNO}_2 + 2(\text{CH}_3)_2\text{NH}$$
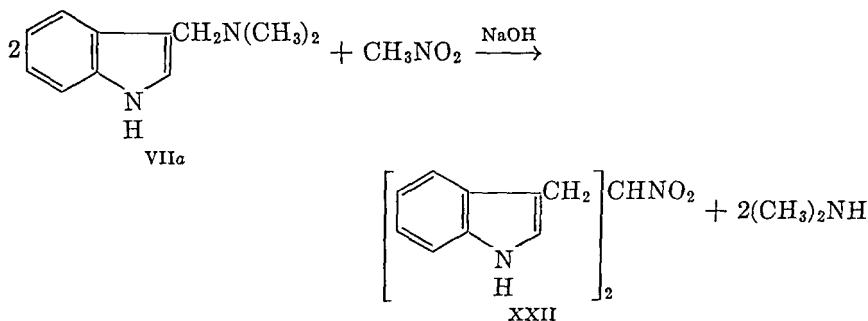
Ethyl nitroacetate is dialkylated with gramine in the presence of ethanol and sodium ethoxide [18] or in the presence of powdered sodium hydroxide in xylene.[19] Skatylnitroacetic ester (XXIII), which can be converted to tryptophan in good yield, is obtained from gramine and ethyl nitroacetate in xylene solution in the absence of any catalyst; [19] diethyl nitromalonate may also be alkylated by means of gramine and the product may be converted to tryptophan.[20]

$$\underset{\text{XXIII}}{\text{(indole ring)}} \text{—CH}_2\text{CHCO}_2\text{C}_2\text{H}_5 \text{, NO}_2$$
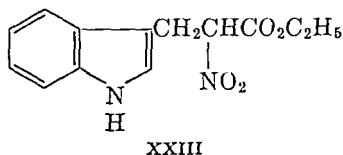
Ketonic Mannich bases react rapidly with nitromethane in the presence of alkaline catalysts, as sodium methoxide or ethanolic potassium hydroxide, to form mono-, di-, or tri-alkylated nitromethanes.[21] Thus, with the Mannich bases of acetone (XXIV), cyclohexanone (XVI), acetophenone (XXV), and 4-methoxy- and 3,4-dimethoxy-acetophenone, monoalkylated products are formed from nitromethane in the presence of sodium ethoxide. Some dialkylated product is formed from the

$$\text{RCOCHCH}_2\text{N(CH}_3)_2 + \text{CH}_3\text{NO}_2 \xrightarrow[-(\text{CH}_3)_2\text{NH}]{\text{Base}}$$
$$\underset{\text{R}'}{|}$$

$$\text{RCOCHCH}_2\text{CH}_2\text{NO}_2, \ (\text{RCOCHCH}_2)_2\text{CHNO}_2, \ \text{or} \ (\text{RCOCHCH}_2)_3\text{CNO}_2$$
$$\underset{\text{R}'}{|} \qquad\qquad\qquad \underset{\text{R}'}{|} \qquad\qquad\qquad\qquad \underset{\text{R}'}{|}$$
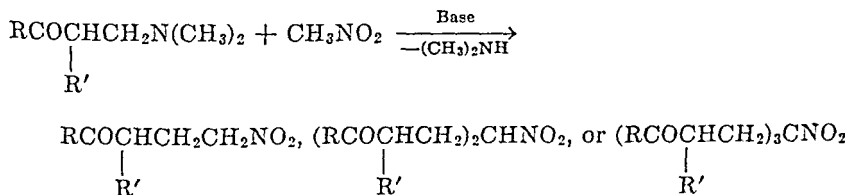
[19] Lyttle and Weisblat, *J. Am. Chem. Soc.*, **69**, 2118 (1947); Weisblat and Lyttle, U. S. pat. 2,557,041 [*C. A.*, **46**, 1593 (1952)].

[20] Weisblat and Lyttle, *J. Am. Chem. Soc.*, **71**, 3079 (1949); U. S. pat. 2,528,928 [*C. A.*, **45**, 3870g (1951)].

[21] Reichert and Posemann, *Arch. Pharm.*, **275**, 67 (1937).

Mannich base of 3,4-dimethoxyacetophenone. Di- and tri-alkylated nitromethanes are formed by reaction of the Mannich base of acetophenone, nitromethane, and ethanolic potassium hydroxide.

$$CH_3COCH_2CH_2NR_2 \qquad C_6H_5COCH_2CH_2NR_2$$
$$XXIV \qquad\qquad XXV$$

1- and 2-Nitropropane can be alkylated by the Mannich base derived from 1-nitropropane.[21a,b] The reaction fails with the Mannich base of 2-nitropropane.

Alkylation of Ketones and β-Keto Esters. Many alkylations of ketones and β-keto esters by means of Mannich bases have been reported.[21c] The principal interest in these reactions has been in the prepa-

[21a] Snyder and Hamlin, *J. Am. Chem. Soc.*, **72**, 5082 (1950).
[21b] Other examples are reported by Gill, James, Lions, and Potts, *J. Am. Chem. Soc.*, **74**, 4923 (1952).
[21c] For more recent examples see Barltrop and Saxton, *J. Chem. Soc.*, **1952**, 1038; Gunstone and Heggie, *ibid.*, **1952**, 1437.

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$$CH_3COCH_2CH_2\overset{+}{N}(CH_3)(C_2H_5)_2 \ I^-$$

It will be noted that the alkylation products of ketones or β-keto esters with a ketonic Mannich base are δ-diketones, many of which can form cyclohexenone derivatives by internal aldol condensation as in the examples cited above. Often, as above, such cyclizations occur during alkylation. These reactions may be used to form simple cyclohexenone derivatives, such as the terpenes carvenone (XXIX) and piperitone [32,32a,32b] (XXX), bicyclic terpenes containing angular methyl groups
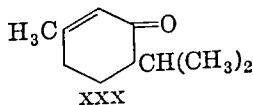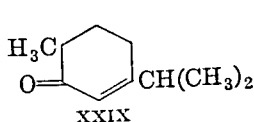
such as the cyperones [33] (XXXI), polynuclear aromatic hydrocarbons,[26] fused ring systems related to the steroids and containing angular methyl groups,[34,35] compounds related to alkaloids and containing angular

[32] Downes, Gill, and Lions, *Australian J. Sci.*, **10**, 147 (1948) [*C. A.*, **42**, 7257 (1948)].
[32a] Downes, Gill, and Lions, *J. Am. Chem. Soc.*, **72**, 3464 (1950).
[32b] Gill and Lions, *J. Am. Chem. Soc.*, **72**, 3468 (1950).
[33] Adamson, McQuillin, Robinson, and Simonsen, *J. Chem. Soc.*, **1937**, 1576; McQuillin, *ibid.*, **1951**, 716.
[34] Martin and Robinson, *J. Chem. Soc.*, **1943**, 491; **1949**, 1866.
[35] Cornforth and Robinson, *J. Chem. Soc.*, **1949**, 1855.

used as the base. Only a few alkylations of a ketone by a free ketonic Mannich base (tertiary amine) have been reported. One is the alkylation of 2-phenylcyclohexanone (XXVIII) with a Mannich base of acetone (XXIV), in the presence of one equivalent of sodium amide, which proceeds in 42% yield.[30] In two other cases, the bases were employed as hydrochlorides with sodium hydroxide or potassium *t*-butoxide as catalyst.

The yield of alkylation product may be increased by formylating the ketone first by means of methyl formate. The resulting α-hydroxymethyleneketone (which is considerably more acidic than the parent ketone) is then alkylated in good yield with the methiodide of the ketonic Mannich base in the presence of sodium methoxide, and the hydroxymethylene group is finally removed by basic cleavage at the same time cyclization is effected.[30a, b]

When a ketone is to be alkylated, there may be two reactive carbon atoms available. It has been found that active methinyl groups are more readily alkylated than active methylene groups. An active methylene group bearing a phenyl group is more readily alkylated than one bearing only alkyl groups. The following examples illustrate these principles.[25, 31]

[30] Boekelheide, *J. Am. Chem. Soc.*, **69**, 790 (1947).
[30a] Wilds and Shunk, *J. Am. Chem. Soc.*, **72**, 2388 (1950); see, however, Woodward et al., *J. Am. Chem. Soc.*, **74**, 4223 (1952).
[30b] Wilds and Werth, *J. Org. Chem.*, **17**, 1149, 1154 (1952).
[31] Crowley and Robinson, *J. Chem. Soc.*, **1938**, 2001.

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$$\text{XXVIII} + (CH_3)_2NCH_2CH_2COCH_3 \longrightarrow$$

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$$R \underset{\overset{HCO_2CH_3}{NaOCH_3}}{\longrightarrow} R \text{—} CHOH \quad + $$

$$CH_3COCH_2CH_2\overset{+}{N}(CH_3)(C_2H_5)_2 \ I^- \xrightarrow{NaOCH_3} R \underset{CHO}{\overset{}{—}} CH_2CH_2COCH_3$$

$$\xrightarrow{NaOH} R$$

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[31] Crowley and Robinson, J. Chem. Soc., 1938, 2001.

In another useful version, the methiodide of 1-methyl-4-piperidone (XXXII), which may be considered as a Mannich base formed from two moles of formaldehyde and one mole each of acetone and methylamine, is used as an alkylating agent.[37] Only one of the carbon-nitrogen bonds breaks, and a 3-keto-5-dimethylaminoamyl group is thus introduced into the compound alkylated.

$$CH_3COCH_2CO_2C_2H_5 \rightarrow \begin{matrix} CH_3COCHCO_2C_2H_5 \\ | \\ CH_2CH_2COCH_2CH_2N(CH_3)_2 \end{matrix}$$

XXXII

The primary products may be capable of cyclization.[37]

Alkylation of Esters. Only esters containing doubly or triply activated carbon atoms have been alkylated by amine replacement reactions. Alkylations of α-nitro esters and β-keto esters have already been described.

Diethyl malonate has been monomethylated by means of tetramethylammonium ethoxide.[38] Diethyl sodiomalonate has been benzylated, in yields as high as 79%, by means of quaternary salts containing, in addition to the benzyl group, methyl, ethyl, phenyl, or pentamethylene groups. Dibutyl ether, absolute ethanol, or an excess of diethyl malonate has been used as a solvent under various temperatures and pressures.[7] Highest yields were obtained from diethyl sodiomalonate with benzyltrimethylammonium bromide in refluxing dibutyl ether (77%) or with benzyldimethylanilinium chloride heated in the absence of solvent (73–79%). Diethyl sodiomalonate has also been alkylated with the methiodides of 1-dimethylaminomethyl-2-methoxynaphthalene [6] (IV, R = CH$_3$) and (+, −)-N,N-dimethyl-α-phenylethylamine,[2] using Diethyl Carbitol as a solvent. When the methiodide of (+)-N,N-dimethyl-α-phenylethylamine (VI) was employed as an alkylating agent, the alkylation product was optically inactive; a small amount of N,N-dimethyl-α-phenylethylamine (probably formed by demethylation of the salt) was recovered from the reaction mixture and found to be only slightly optically active.[2]

Methyl cyanoacetate and tricarbethoxymethane have been benzylated with benzyldimethylamine.[39] The initial step in this reaction is a

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[38] Wittig, Heintzeler, and Wetterling, *Ann.*, 557, 201 (1947).
[39] Snyder, Eliel, and Carnahan, *J. Am. Chem. Soc.*, 72, 2958 (1950).

ethyl [36] or phenyl [30] groups, or phenols possessing *meta* bridges.[27] Further examples of this type of alkylation are listed in Table VII.

α-Cyperone
XXXIa

β-Cyperone
XXXIb
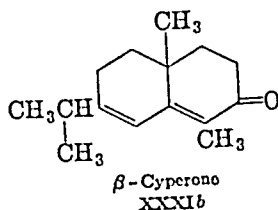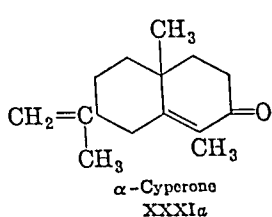
An interesting modification of this reaction consists in the use of the di-Mannich base of acetone; the simple alkylation product undergoes amine elimination to form a compound that can be cyclized to a dienone capable of rearranging to a phenol.[26, 27, 27a] Whether an *ortho*- or *meta*-bridged phenol is obtained depends on the size of the alicyclic ring.[27a]
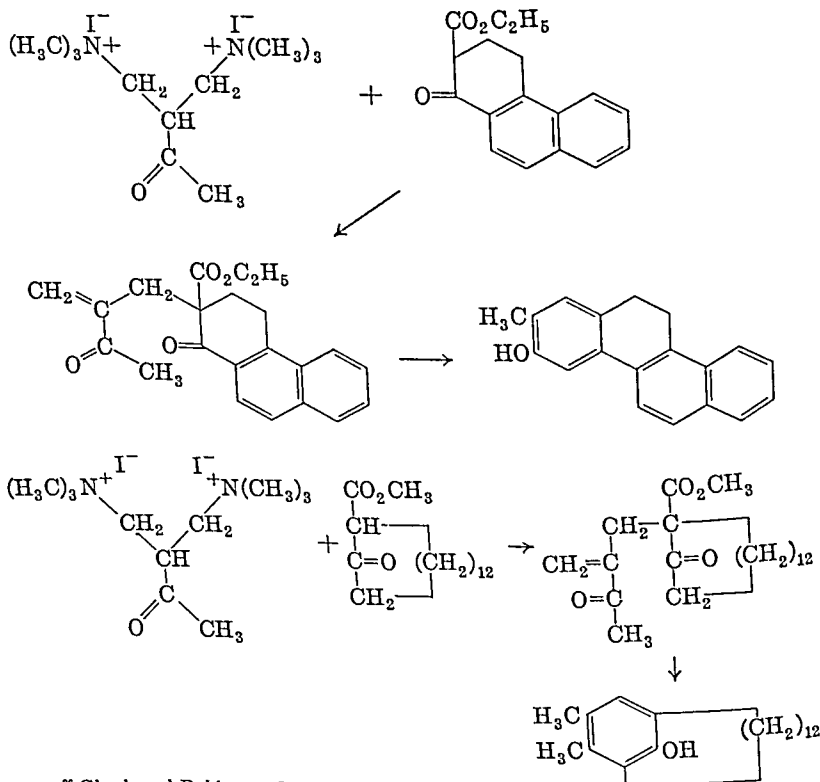
[36] Ghosh and Robinson, *J. Chem. Soc.*, **1944**, 506.

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$$CH_2=C$$

α-Cyperone
XXXI*a*

β-Cyperone
XXXI*b*

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$$(H_3C)_3N^+ \quad +N(CH_3)_3$$

$$CO_2C_2H_5$$

$$CO_2CH_3$$
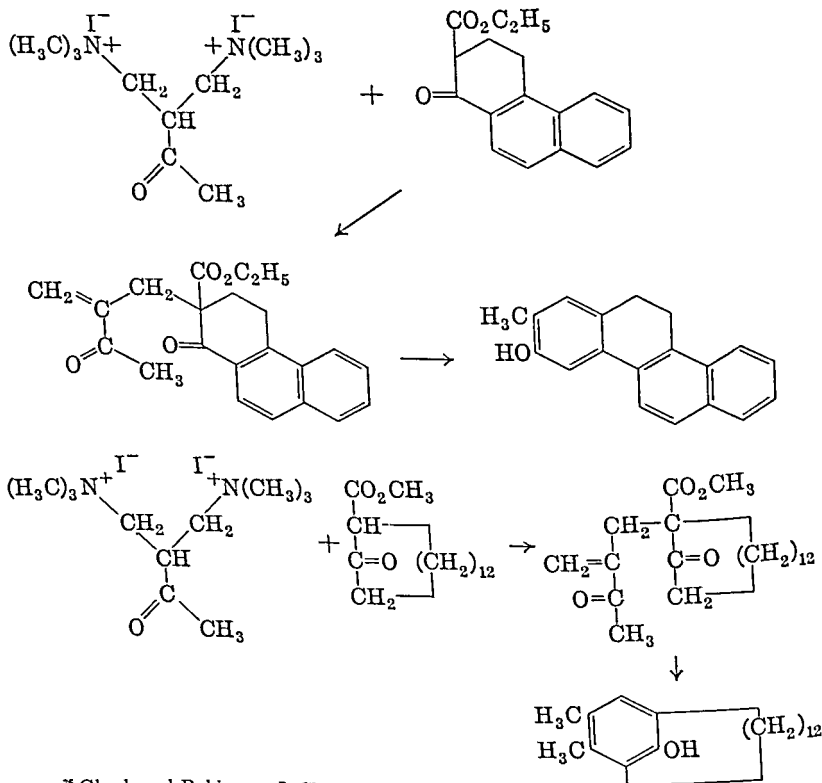
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[39] Snyder, Eliel, and Carnahan, *J. Am. Chem. Soc.*, **72**, 2958 (1950).

(B)

$$\text{indole-CH}_2\text{N(CH}_3)_2 + \text{Na} \overset{X}{\underset{Y}{\text{C}}}\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{C}_2\text{H}_5\text{I}}$$

$$\text{indole-CH}_2\overset{X}{\underset{Y}{\text{C}}}\text{CO}_2\text{C}_2\text{H}_5 + \text{NaI} + \overset{+}{\text{N}}(\text{CH}_3)_2(\text{C}_2\text{H}_5)_2 \text{ I}^-$$

(C)

$$\text{indole-CH}_2\text{N(CH}_3)_2 + \text{H}\overset{X}{\underset{Y}{\text{C}}}\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{(NaOH)}}$$

$$\text{indole-CH}_2\overset{X}{\underset{Y}{\text{C}}}\text{CO}_2\text{C}_2\text{H}_5 + \text{HN(CH}_3)_2$$

$$X = -CO_2C_2H_5, -CN, \text{ etc.}$$
$$Y = -H, -R, -NHCOR, -CO_2C_2H_5, \text{ etc.}$$

The Mannich bases of indole, such as gramine (VIIa), have been used in alkylations of cyanoacetic and malonic esters. Yields of 85% were obtained by method A,[7] whereas by method C a 76% yield was obtained in the alkylation of malonic ester.[7] Tricarbethoxymethane, in the absence of added catalyst, has been alkylated by gramine (procedure C, 67% yield).[17]

1-Methylgramine (XXI) can be used as an alkylating agent for malonic ester derivatives (procedure C), although yields are low (9–15%); again the ester acts as a quaternizing agent in these reactions, since tertiary amines containing the alkyl group of the ester are formed.[39] Added base seems to decrease the rate of the reaction without appreciably reducing the yields. Higher yields are obtained by use of the methiodide of 1-methylgramine and the sodio derivative of the malonic ester; best yields are obtained with cyanomalonic ester (51%) and tricarbethoxymethane.[17] In these last two reactions water may be used as a solvent since the active methylene compounds are more acidic than water.

(B)

(C)

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or diethyl benzamidomalonate (XLIII).[47]   The methiodide of 1-methyl-gramine (XXI) reacts with the sodium salt of acetamidocyanoacetic ester (XLV); the product, obtained in 69% yield, can be hydrolyzed to 1-methyltryptophan (XLVI).[48]

$$RCH_2CH(NH_2)CO_2H$$

XXXVIII   R =

XXXIX   R =

XL   R =

XLI $R_1 = H$, $R_2 = CH_3CO$

XLII $R_1R_2 =$

XLIII $R_1 = H$, $R_2 = C_6H_5CO$

XLIV

XLVI

$$CH_3CONHCHCO_2C_2H_5$$
$$\quad\quad\quad\quad\quad CN$$

XLVII

XLV
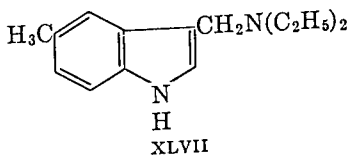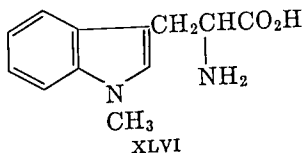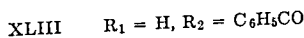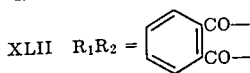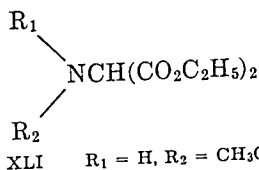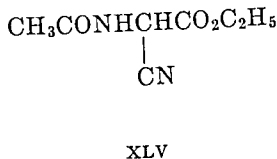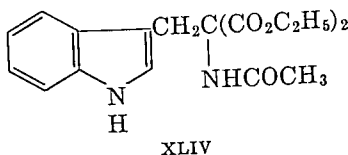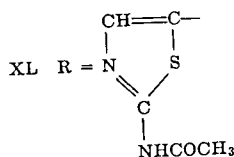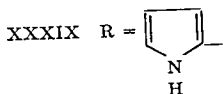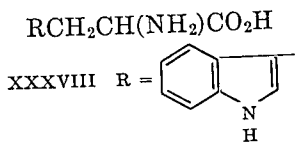
Better yields of alkylation product are claimed when the quaternary salt is formed *in situ* (method B) by addition of two equivalents of ethyl iodide or dimethyl sulfate to a cooled mixture of the Mannich base with the sodio derivative of an amidomalonic ester in absolute ethanol.[40] Thus, with gramine (VIIa) and ethyl acetamidocyanoacetate (XLV) or diethyl acetamidomalonate (XLI) yields of 98% and 95% have been reported.[40,49,50]   Yields of 79–93% have been reported in alkylations of diethyl acetamidomalonate by this method with 2-, 4-, 5-, 6-, and 7-methylgramine.[51]   Ethyl acetamidocyanoacetate (XLV) was alkylated

[47] Albertson, Archer, and Suter, *J. Am. Chem. Soc.*, **66**, 500 (1944).

[48] Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948).

[49] Albertson and Tullar, *J. Am. Chem. Soc.*, **67**, 502 (1945).

[50] Albertson, Archer, and Suter, U. S. pats. 2,451,310 and 2,468,912 [*C. A.*, **43**, 1442, 5806 (1949)].

[51] Rydon, *J. Chem. Soc.*, **1948**, 705; Rydon and Siddapa, *ibid.*, **1951**, 2462; Kornfeld, *J. Org. Chem.*, **16**, 806 (1951); Hamlin and Fischer, *J. Am. Chem. Soc.*, **73**, 5007 (1951).

With 1-methylgramine (XXI), excess diethyl acetamidomalonate (XLI), and sodium, a total yield of only 12.5% of alkylation products is obtained.[17]

2-Dimethylaminomethylpyrrole reacts with diethyl acetamidomalonate (XLI) in toluene or xylene in the presence of sodium hydroxide to give a 70–80% yield of a product having the structure L.[43]

XLIX   L

Diethyl malonate reacts slowly with Mannich bases of acetone [56] (XXIV) and cyclohexanone [57] at room temperature in ethanol containing small amounts of sodium ethoxide to form the normal simple alkylation products in yields of 43% and 86%, respectively. A rather low yield (16%) of ethyl 2-carbethoxy-5-ketohexanoate (LI) was obtained by reaction of diethyl sodiomalonate with the methiodide of 1-morpholino-3-butanone (LII).[58] Powdered sodium hydroxide in xylene, as used in gramine alkylations (method C, p. 100), served as catalyst in an alkylation of diethyl malonate with a Mannich base of 2-phenylcyclohexanone (50% yield).[58a]

$$CH_3COCH_2CH_2CH(CO_2C_2H_5)_2 \qquad\qquad CH_3COCH_2CH_2N\!\!<\text{(morpholino)}$$

LI   LII

Reactions of ketonic Mannich bases with derivatives of aminomalonic ester or tricarbethoxymethane have not been reported. However, the following intramolecular reaction with a derivative of acetamidomalonic ester has led to a cyclopropane derivative.[58b]

   (33%)

Methyl and ethyl cyanoacetate have been alkylated with the Mannich bases of 1-nitropropane, but the yields are not high (16–23%).[21a]

[56] Mannich and Fourneau, *Ber.*, **71**, 2090 (1938).
[57] Mannich and Koch, *Ber.*, **75**, 803 (1942).
[58] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939) [*C. A.*, **33**, 5855 (1939)].
[58a] Bachmann and Wick, *J. Am. Chem. Soc.*, **72**, 3388 (1950).
[58b] Rinderknecht and Niemann, *J. Am. Chem. Soc.*, **73**, 4259 (1951).

by 3-diethylaminomethyl-5-methylindole (XLVII) in 87% yield by this method.[52]

Yields of 90–94% were reported in alkylations by pyrrole Mannich bases of ethyl acetamidocyanoacetate (XLV) and diethyl acetamidomalonate (XLI), but a low yield was obtained with diethyl phthalimidomalonate (XLII).[43] Reaction of two moles of diethyl acetamidomalonate (XLI) with 2,5-bis(dimethylaminomethyl)pyrrole (XLVIII) occurs quantitatively by this method.[44]

$$(CH_3)_2NH_2C\underset{\underset{\underset{XLVIII}{H}}{N}}{\boxed{}}CH_2N(CH_3)_2 + 2CH_3CONHCH(CO_2C_2H_5)_2 \rightarrow$$

XLI

$$(H_5C_2O_2C)_2CH_2C\underset{\underset{CH_3CONH\quad H}{N}}{\boxed{}}CH_2C(CO_2C_2H_5)_2$$

NHCOCH_3
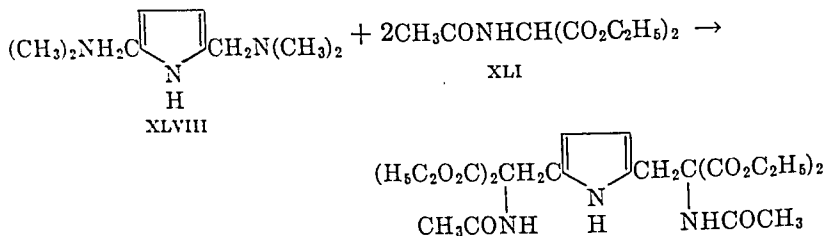
2-Acetamido-5-dimethylaminomethylthiazole (XXXVII, R = H) and the 4-methyl homolog (XXXVII, R = CH₃) have been used in alkylations of diethyl acetamidomalonate (XLI) in the presence of dimethyl sulfate.[41] Of interest in this case is the use of the Mannich base hydrochloride, together with a molar excess of sodium ethoxide (to neutralize the hydrogen chloride).

Method C gives good yields in alkylations of aminomalonic ester derivatives with indole Mannich bases. Diethyl skatylacetamidomalonate (XLIV) is obtained in 90% yield when gramine (VIIa) and diethyl acetamidomalonate (XLI) are heated in xylene with powdered sodium hydroxide.[41] Lower yields are obtained in pyridine, in the absence of a solvent, or in the absence of a catalyst. Good to moderate yields are obtained when gramine (VIIa) is replaced by 3-diethylaminomethylindole (VII, R = C₂H₅) (85% yield) or 3-piperidinomethylindole (64%). Diethyl phthalimidomalonate (XLII) is alkylated to only a slight extent (10%) under the best of these conditions, but diethyl formamidomalonate gives the alkylation product in excellent yield (98%).[52] Satisfactory yields of alkylation products have been obtained by this method in alkylations of diethyl acetamidomalonate (XLI) and ethyl acetamidocyanoacetate (XLV) with 5-bromogramine,[53] 6-methylgramine,[54] and 3-diethylaminomethyl-2-carbethoxyindole (XLIX).[55]

With 1-methylgramine (XXI), excess diethyl acetamidomalonate (XLI), and sodium, a total yield of only 12.5% of alkylation products is obtained.[17]

2-Dimethylaminomethylpyrrole reacts with diethyl acetamidomalonate (XLI) in toluene or xylene in the presence of sodium hydroxide to give a 70–80% yield of a product having the structure L.[43]

XLIX

L

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$$CH_3COCH_2CH_2CH(CO_2C_2H_5)_2 \qquad CH_3COCH_2CH_2N\langle O$$

LI

LII

Reactions of ketonic Mannich bases with derivatives of aminomalonic ester or tricarbethoxymethane have not been reported. However, the following intramolecular reaction with a derivative of acetamidomalonic ester has led to a cyclopropane derivative.[58b]

Methyl and ethyl cyanoacetate have been alkylated with the Mannich bases of 1-nitropropane, but the yields are not high (16–23%).[21a]

[56] Mannich and Fourneau, Ber., **71**, 2090 (1938).

[57] Mannich and Koch, Ber., **75**, 803 (1942).

[58] Harradence and Lions, J. Proc. Roy. Soc. N. S. Wales, **72**, 233 (1939) [C. A., **33**, 5855 (1939)].

[58a] Bachmann and Wick, J. Am. Chem. Soc., **72**, 3388 (1950).

[58b] Rinderknecht and Niemann, J. Am. Chem. Soc., **73**, 4259 (1951).

An Alkylation of Indole

Indole reacts with diethyl piperidinomethylformamidomalonate to give diethyl skatylformamidomalonate [59] which is readily hydrolyzed to tryptophan in one step.[52a] The alkylation proceeds best in xylene
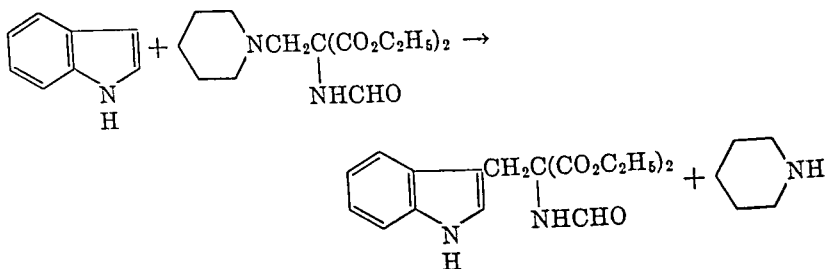
solution with a sodium hydroxide catalyst (76%); lower yields are obtained in other aromatic hydrocarbon solvents. In the absence of the basic catalyst, 3-piperidinomethylindole (VII, R_2 = pentamethylene) is the principal or exclusive product. Other alkylations with Mannich bases of formamidomalonic ester have been reported.[59a,b] Indole has also been alkylated with diethylaminoacetonitrile.[59c]

Amine Replacement Reactions of Quaternary Salts with Organometallic Compounds

Only a few reactions of Grignard and organolithium reagents with quaternary ammonium salts resulting in displacement of the ammonium nitrogen by the alkyl group of the organometallic reagent are on record. The reaction apparently has not been studied extensively. 9-Fluoryllithium reacts with tetramethylammonium chloride to yield 9-methylfluorene in unspecified yield.[38] Phenyllithium reacts in a different fashion.[60] From the reaction of phenyllithium with benzyltrimethylammonium bromide, no diphenylmethane was isolated; the latter was apparently metallated as formed and further alkylated by the quaternary salt to 1,1,2-triphenylethane. α-Phenylethyldimethylamine was

[59] Butenandt, Hellmann, and Renz, Z. physiol. Chem., **284**, 175 (1949); C. Y. Meyers, doctoral thesis, University of Illinois, Urbana, Ill., 1951.

[59a] Hellmann and Brendle, Z. physiol. Chem., **287**, 235 (1951).

[59b] Hellmann and Renz, Chem. Ber., **84**, 901 (1951).

[59c] N. J. Murphy, bachelor's thesis, University of Notre Dame, Notre Dame, Ind., 1952.

[60] Wittig and co-workers, Ann., **555**, 133 (1944); **557**, 193 (1947). For a review see: Wittig, Angew. Chem., **63**, 15 (1951).

also obtained.[61]   The methiodide of 1-methylgramine (XXI) reacts with methylmagnesium iodide and with phenylmagnesium bromide in refluxing dibutyl ether to yield 1-methyl-3-ethylindole (LIII) and

$$C_6H_5Li + C_6H_5CH_2\overset{+}{N}(CH_3)_3\ Br^- \rightarrow LiBr + N(CH_3)_3 + C_6H_5CH_2C_6H_5$$

$$C_6H_5CH_2C_6H_5 + C_6H_5Li \rightarrow C_6H_6 + C_6H_5CHLiC_6H_5$$

$$C_6H_5CHLiC_6H_5 + C_6H_5CH_2\overset{+}{N}(CH_3)_3\ Br^- \rightarrow$$

$$LiBr + N(CH_3)_3 + C_6H_5CH_2CH(C_6H_5)_2$$
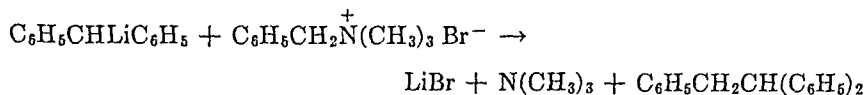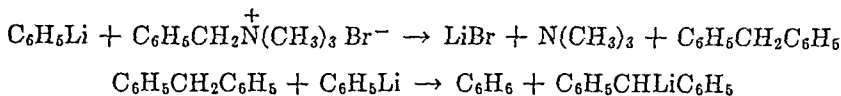
1-methyl-3-benzylindole (LIV).[62]   The methiodide of gramine (VIIa) similarly yields 3-ethylindole (LV), 3-benzylindole (LVI), and 3-phenethylindole (LVII), although in poor yield; a by-product with the composition and properties of sym-3,3-diindolylethane (LVIII) is presumably formed by a coupling reaction (equation on p. 133). 3-Benzylindole was obtained in only 3% yield when the tertiary amine gramine was treated with phenylmagnesium bromide. Attempts to extend the reaction with organometallic reagents to a number of other Mannich bases and quaternary salts were unsuccessful.[62]   N,N'-Benzaldipiperidine (LIX,

LIII $R_1 = CH_3$, $R_2 = C_2H_5$
LIV $R_1 = CH_3$, $R_2 = C_6H_5CH_2$
LV $R_1 = H$, $R_2 = C_2H_5$
LVI $R_1 = H$, $R_2 = C_6H_5CH_2$
LVII $R_1 = H$, $R_2 = C_6H_5CH_2CH_2$

LVIII
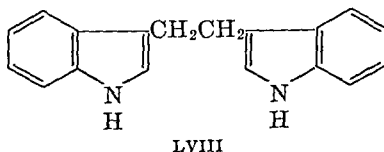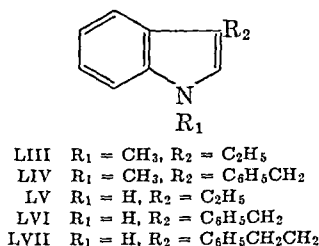
R = H) and N,N'-benzaldi-γ-pipecoline (LIX, R = CH₃) react with benzylmagnesium   chloride   to   give   1-piperidino-1,2-diphenylethane (LX, R = H) and 1-(γ-pipecolino)-1,2-diphenylethane (LX, R = CH₃) in 18 and 14% yield, respectively.[63]

[61] Wittig, Mangold, and Felletschin, *Ann.*, **560**, 116 (1948).
[62] Snyder, Eliel, and Carnahan, *J. Am. Chem. Soc.*, **73**, 970 (1951).
[63] Goodson and Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).

$$C_6H_5CH \begin{array}{c} \overset{\displaystyle N}{\bigcirc} R \\ \underset{\displaystyle N}{\bigcirc} R \end{array} \quad + \; C_6H_5CH_2MgCl \; \rightarrow$$

LIX

$$C_6H_5CH \overset{\displaystyle \overset{N}{\bigcirc} R}{\underset{CH_2C_6H_5}{|}} \quad + \; R \overset{\displaystyle }{\bigcirc} NMgCl$$

LX
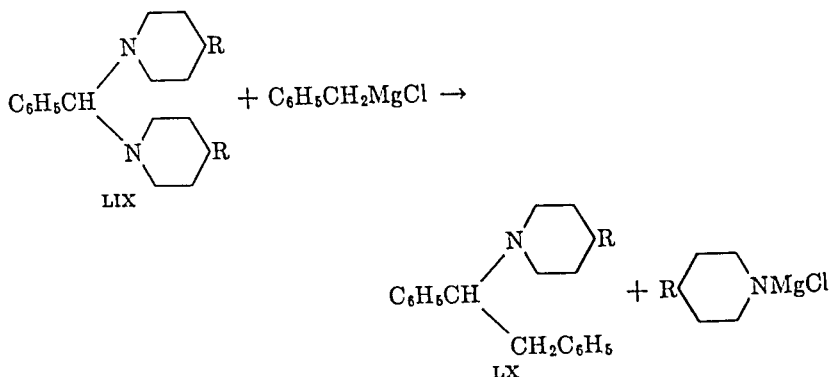
MECHANISM OF THE REACTION

The path by which alkylations with tertiary amines and quaternary ammonium salts proceed has not yet been definitely established, and any statements concerning the mechanism of the reaction are therefore speculative.

Alkylations with Tertiary Amines

The mechanism that has most frequently been proposed for alkylations with tertiary amines involves the elimination of a secondary amine, resulting in the formation of an unsaturated compound which undergoes addition of the species to be alkylated.

$$ACH_2CH_2NR_2 \; \rightarrow \; NHR_2 + ACH{=}CH_2$$

$$ACH{=}CH_2 + CHRR'R'' \; \rightarrow \; ACH_2CH_2CRR'R''$$
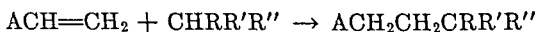
A scheme of this type was first proposed for alkylations with phenolic Mannich bases by von Auwers.[64-68] The hypothetical intermediate is a methylenequinone whose formation involves 1,4- or 1,6-elimination.
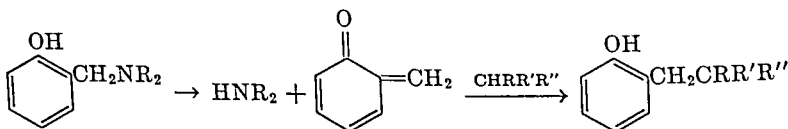
[64] v. Auwers, *Ber.*, **36**, 1878 (1903).
[65] v. Auwers, *Ann.*, **344**, 131 (1906).
[66] v. Auwers and Bullmann, *Ber.*, **59**, 2719 (1926).
[67] Snyder and Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948).
[68] Dalgliesh, *J. Am. Chem. Soc.*, **71**, 1697 (1949).
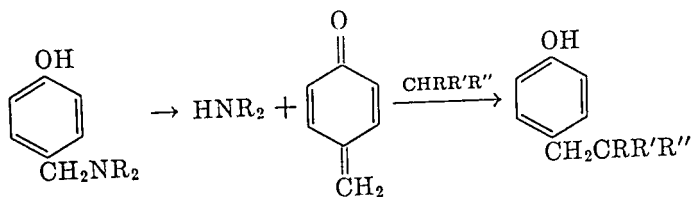
A similar scheme has been proposed [9] for alkylations with gramine (VIIa).
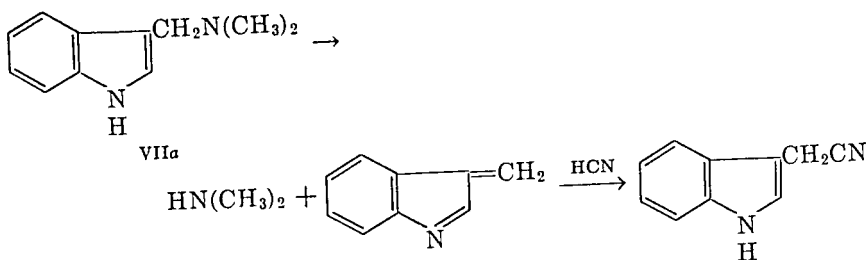
1,2-Elimination may be the first step in alkylations with ketonic Mannich bases.[24]
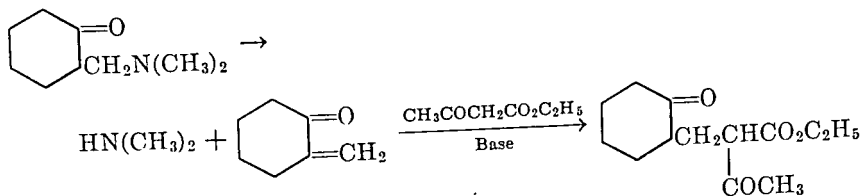
For the ketonic Mannich bases, the elimination-addition mechanism is supported by the facts that these compounds will yield α,β-unsaturated ketones by elimination of secondary amines [61, 69, 70, 71] and that α,β-unsaturated ketones will add active methylene compounds (Michael reaction).

The elimination of the secondary amine may be either an acid-catalyzed E_1 (mechanism A) or a base-catalyzed E_2 (mechanism B) reaction.[72] In the simple elimination reactions of ketonic Mannich

[69] Mannich and co-workers, *Ber.*, **53**, 1874 (1920); **55**, 356, 3510 (1922); **57**, 1116 (1924); **74**, 554 (1941).

[70] Mannich and Hönig, *Arch. Pharm.*, **265**, 598 (1927).

[71] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 284 (1939) [*C. A.*, **33**, 6825 (1939)].

[72] Remick, *Electronic Interpretations of Organic Chemistry*, 2nd ed., p. 424, John Wiley & Sons, 1949.

(A) $ACH_2CH_2NR_2 + H^+ \rightarrow ACH_2CH_2NR_2H^+ \rightarrow$

$NHR_2 + ACH_2CH_2^+ \rightarrow ACH{=}CH_2 + H^+$

(B) $ACH_2CH_2NR_2 + B\text{:} \rightarrow A\overset{-}{C}HCH_2NR_2 + BH^+$

$A\overset{-}{C}HCH_2NR_2 \rightarrow ACH{=}CH_2 + NR_2^-$

$NR_2^- + BH^+ \rightarrow NHR_2 + B\text{:}$
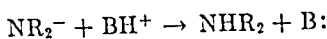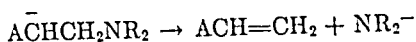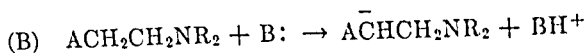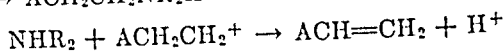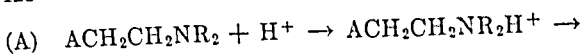
bases, both acid catalysis [69, 70] and base catalysis [61, 73] have been observed. It is also possible that reaction occurs between two molecules of the Mannich base, one acting as an acid and the other as a base. Still another possibility with ketonic and *ortho*-substituted phenolic Mannich bases is an *intra*molecular elimination involving a chelate intermediate.
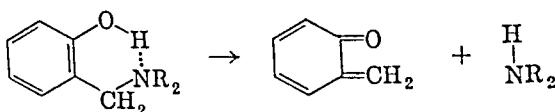
Only the enolic form of a ketonic Mannich base is capable of chelation.
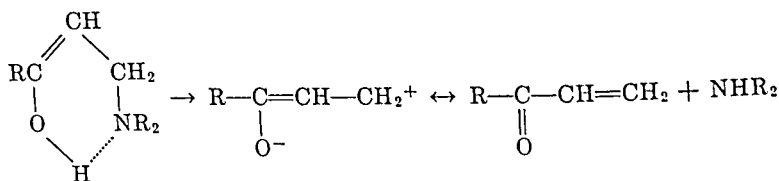
An attempt to obtain spectral evidence for the existence of this type of intermediate has, however, failed.[74]

The Michael addition of an active methylene compound to an activated unsaturated species is known to be base catalyzed. The over-all alkylation reaction would therefore be expected to be either base or acid-base catalyzed, and this is actually found to be so. Since one of the reactants is itself quite basic, the addition of an extrinsic basic catalyst is sometimes unnecessary or even undesirable.[17, 19, 20] In the alkylation of dibenzoylmethane by 1-morpholinomethyl-2-naphthol (XXVII), the reaction is known to be catalyzed by added hydrochloric acid.[23]

The facts that benzyldimethylamine and 1-methylgramine (XXI) will alkylate methyl cyanoacetate and tricarbethoxymethane and that 1-methylgramine will alkylate diethyl acetamidomalonate (XLI),[17, 39] although these amines are structurally incapable of reacting by an

[73] Bruylants, *Bull. soc. chim. Belg.*, **32**, 256 (1923).
[74] Brewster, unpublished observations.

elimination-addition mechanism, have been satisfactorily explained by demonstrating that alkylation is preceded by quaternization [39] (p. 118). However, 1-methylgramine (XXI) also alkylates secondary amines [75] and 1-methylindole,[17] and these reactions (like the reaction of 2-dimethylaminomethyl-2-nitropropane with piperidine [21a]) cannot be explained as alkylations with quaternary salts; they will take place only in the presence of acids [75] and might therefore proceed by a path resembling that of mechanism A above (p. 128). It should be noted that one of the intermediates in this mechanism is a carbonium ion and that the loss of a proton from this ion to form the unsaturated compound is not essential, since the carbonium ion itself could be the alkylating agent.

(indole with CH$_2$N(CH$_3$)$_2$ at 3-position, N-CH$_3$) + H$^+$ → (indole with CH$_2$NH(CH$_3$)$_2^+$ at 3-position, N-CH$_3$) →

NH(CH$_3$)$_2$ + (indole with CH$_2^+$ at 3-position, N-CH$_3$)

(indole with CH$_2^+$ at 3-position, N-CH$_3$) + $^-$CRR'R'' → (indole with CH$_2$CRR'R'' at 3-position, N-CH$_3$)
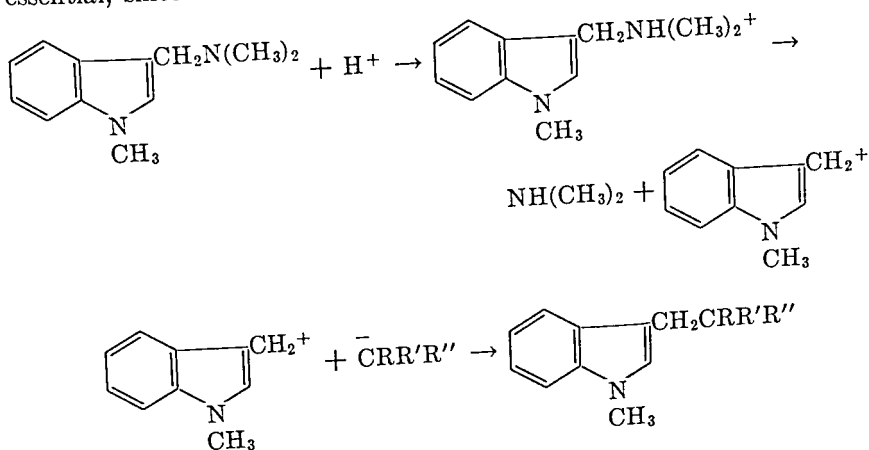
One would expect the carbonium ion postulated in this mechanism to be stabilized by resonance.

(indole with CH$_2^+$ at 3-position, N-CH$_3$) ↔ (indole with =CH$_2$ at 3-position, N$^+$-CH$_3$)
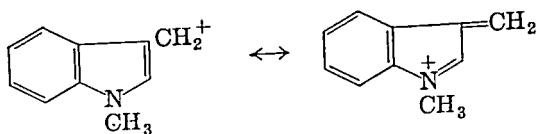
Other types of Mannich bases may react by the same path.

Another possible path for the alkylation reactions with 1-methylgramine hydrochloride, the hydrochloride of 2-dimethylaminomethyl-2-nitropropane (p. 139) and the Mannich base of diethyl formamido-malonate (p. 124), none of which can react by elimination-addition, is a complete reversal of the Mannich reaction,[58a, 68, 76, 77] followed by re-

[75] Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 4233 (1948).
[76] Mannich and Kather, *Arch. Pharm.*, **257**, 18 (1919).
[77] Kermack and Muir, *J. Chem. Soc.*, **1931**, 3089.

combination of the fragments. This may also be the path of alkylations with diethylaminoacetonitrile.[59a, c]
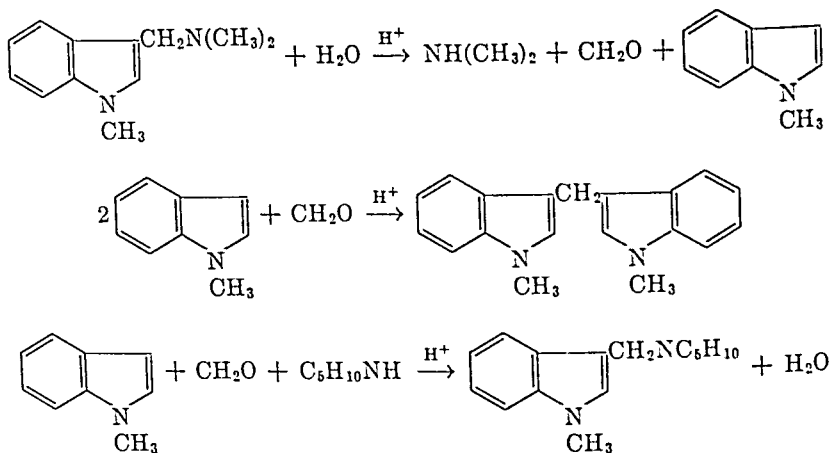
As a further possibility, alkylation reactions with tertiary amines may involve a nucleophilic displacement. Such a path seems less likely in

$$RCH_2\underset{H}{N}(CH_3)_2{}^+ + B^- \rightarrow RCH_2B + NH(CH_3)_2$$
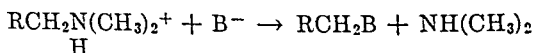
view of the fact that the base would be expected to abstract a proton from the ammonium salt rather than displace a dimethylamine molecule.

Alkylations with Quaternary Salts

It has been proposed that alkylations with quaternary salts of ketonic Mannich bases proceed by the same elimination-addition mechanism as alkylations with the Mannich bases themselves. The elimination step might be of the E_1 type (loss of a tertiary amine followed by loss of a proton) or of the E_2 type (abstraction of a proton followed by loss of a tertiary amine). β-Dimethylaminopivalophenone (XV), a ketonic Mannich base that is structurally incapable of undergoing amine elimination, will not act as an alkylating agent.[11] On the other hand there are numerous quaternary ammonium salts that act as alkylating agents although they show no tendency to undergo amine elimination, viz., quaternary salts of benzyldialkylamines,[4, 6, 7, 39] substituted benzyldialkyl-amines,[2, 6] and 1-methylgramine (XXI).[9, 17, 48] It therefore appears that elimination-addition is not the only path by which alkylation reactions

with quaternary bases may proceed, the alternative being direct substitution. It might be noted that β-dimethylaminopivalophenone (XV) is an amine of the neopentyl type and would therefore not be expected to undergo bimolecular substitution reactions readily.

The question whether the substitution is of the S_N1 or S_N2 type [78] has not been answered definitely for carbon-carbon alkylations. It has been found that the pyrolysis of (+)-α-phenylethyltrimethylammonium acetate to α-phenylethyl acetate proceeds with complete or almost complete inversion,[2] but in carbon alkylations with the active quaternary iodide, VI, both the product and recovered starting material were racemized.[2] Thus, although the reaction of the quaternary acetate is of the S_N2 type, no conclusions can be arrived at with regard to the mechanism of the carbon alkylation since racemization may have been due to abstraction of a proton from the α-carbon by the basic catalyst with concomitant loss of asymmetry. Dipolar ions of the type represented by LXI and known as "alkylides" have been observed in other in-

$$C_6H_5CHN(CH_3)_3{}^+ + B:^- \rightarrow C_6H_5\overset{-}{C}N(CH_3)_3{}^+ + B:H$$

$$\underset{CH_3}{|} \qquad\qquad\qquad \underset{\underset{LXI}{CH_3}}{|}$$
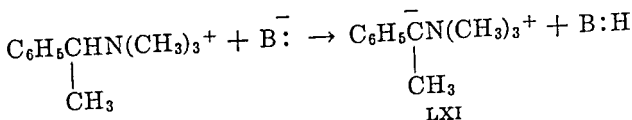
stances;[38, 60] a similar ion is probably responsible for the racemization of optically active nicotine dimethiodide (LXII) by aqueous base at 100°.[61, 79]

LXII
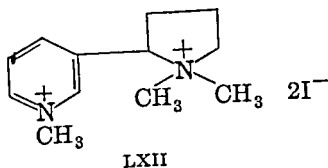
Allylic rearrangements have been observed in alkylations of sodium cyanide with the methiodide of 1-methylgramine (IX) [9] (p. 107) and furfuryltrimethylammonium iodide [10] (p. 107). It is of interest that the ratio of rearranged to normal product in the latter reaction is much smaller than in the alkylation of sodium cyanide with furfuryl chloride.[80, 81] Whereas it formerly was thought that allylic rearrangements were indicative of carbonium-ion intermediates, it is now recognized that they may occur even in reactions that are subject to second-order

[78] See ref. 72, p. 74.
[79] Späth and Bobenberger, Ber., 77, 362 (1944).
[80] Runde, Scott, and Johnson, J. Am. Chem. Soc., 52, 1284 (1930).
[81] Reichstein, Ber., 63, 749 (1930).

kinetics.[82]   Therefore the occurrence of such rearrangements in alkylations with quaternary ammonium salts is not necessarily indicative of an S_N1 (carbonium ion) mechanism.

Further experimentation is needed for definite elucidation of the exact mechanism by which these reactions proceed.

RELATED REACTIONS

It seems desirable, for the sake of completeness, to describe briefly the more important reactions of carbon, nitrogen, oxygen, sulfur, and halogen alkylation by amine replacement, which for various reasons have not been considered in detail in the preceding sections and are omitted from the tables. The following résumé does not pretend to be complete, and only leading references are listed.

Carbon-Carbon Alkylations

The carbon-carbon alkylation reactions of labile amino compounds that were not reviewed in detail fall into the following five categories: (a) those in which intermolecular "self-alkylation" occurs; (b) those in which intramolecular "self-alkylation" or rearrangement occurs; (c) those in which the carbon-nitrogen bond broken is one of the bonds of a heteroaromatic system; (d) those in which the carbon-nitrogen bond broken is found in a diaminomethane; (e) those in which the new carbon-carbon bond formed is part of an ethylenic double bond. Examples of each of the more important types of these reactions are given below.

Intermolecular Self-Alkylations. *Self-Alkylation of Phenolic and Indole Mannich Bases.* Auwers and his co-workers [14, 64, 66, 83-85] found that o- and p-hydroxybenzylamines (many of which cannot be made by the Mannich reaction) readily form diarylmethanes by the loss of formaldehyde and two moles of amine in weakly alkaline solution, according to the equation on p. 109. This reaction is prominent in attempts to use phenolic Mannich bases as alkylating agents.[12,15]   A similar reaction occurs when 1-methylgramine (XXI) is used in alkylations of malonic ester derivatives or when the hydrochloride or methiodide of 1-methylgramine is heated in dilute aqueous alkali.[17]   The Mannich bases ob-

[82] Kepner, Winstein, and Young, *J. Am. Chem. Soc.*, **71**, 115 (1949).

[83] v. Auwers and Senter, *Ber.*, **29**, 1120 (1896).

[84] v. Auwers and co-workers, *Ber.*, **28**, 2910 (1895); **29**, 1110 (1896).

[85] v. Auwers and co-workers, *Ann.*, **344**, 141, 171, 194, 227, 257 (1906).

tained by condensing indoles, benzaldehyde, and aromatic amines undergo similar reactions when heated with dilute hydrochloric acid.[86, 87, 88]

Self-Alkylation of 9-Fluoryltrimethylammonium Hydroxide. Trimethylfluorylammonium hydroxide forms, among other products, dibiphenyleneethylene when heated.[89] The hydrogen atom at the 9 position of the fluorene residue is activated by two aromatic residues and a quaternary ammonium grouping; this hydrogen atom is probably replaced in an alkylation process. The primary product formed by such a reaction is a quaternary ammonium hydroxide, which would be expected to undergo a particularly easy amine elimination. (See ref. 91a for a similar reaction.)
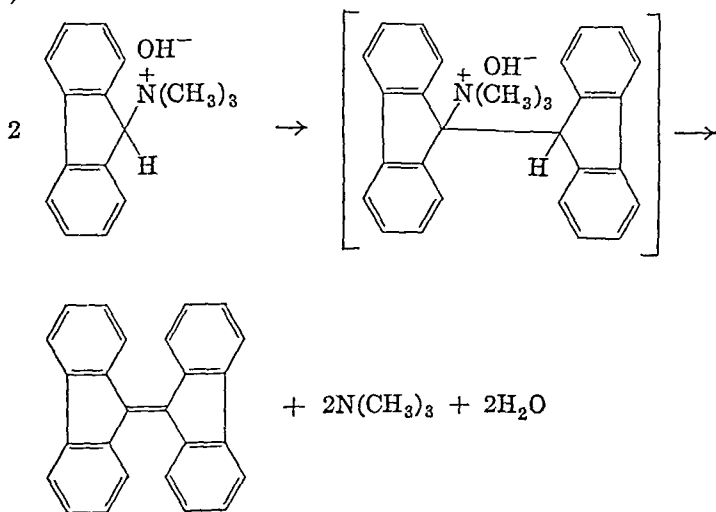
Coupling of Quaternary Ammonium Salts. When quaternary salts of gramine [62] (VIIa) or benzhydryldimethylamine [61] are treated with organometallic reagents, one of the reactions that occurs is coupling of the reactive alkyl residues of the amines.

$$2R\overset{+}{N}(CH_3)_3 \ X^- + 2R'M \rightarrow R{-}R + R'{-}R' + 2N(CH_3)_3 + 2MX$$
$$R = \text{benzhydryl or skatyl}$$
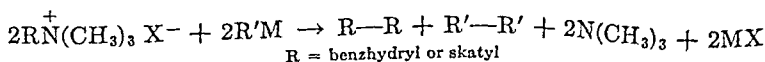
This reaction resembles the coupling of benzyl halides by *Grignard* reagents.

[86] Passerini and Bonciani, *Gazz. chim. ital.*, **63**, 138 (1933).
[87] Passerini and Albani, *Gazz. chim. ital.*, **65**, 933 (1935).
[88] Neri, *Gazz. chim. ital.*, **64**, 420 (1934).
[89] Ingold and Jessop, *J. Chem. Soc.*, **1929**, 2357; **1930**, 713.

Reductive Coupling of Ethanolamines. This rather specific reaction was discovered by Wittig and co-workers.[61]

$$2(C_6H_5)_2COHCH_2N(CH_3)_2 + 6K \rightarrow$$

$$(C_6H_5)_2CHCH_2CH_2CH(C_6H_5)_2 + 2K_2O + 2KN(CH_3)_2$$
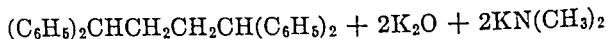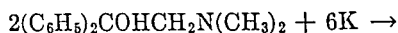
Intramolecular Self-Alkylations. *The Stevens Rearrangement.*[60, 61, 89a-91]

$$C_6H_5COCH_2\overset{+}{N}(CH_3)_2CH_2C_6H_5 + KOH \rightarrow$$
$$I^-$$

$$ N(CH_3)_2$$
$$ |$$
$$ C_6H_5COCHCH_2C_6H_5 + KI + H_2O$$
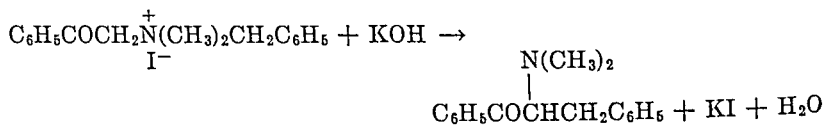
The Sommelet Rearrangement.[61, 91a, 92]
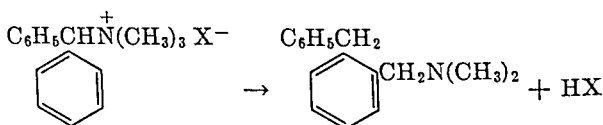
The Hofmann-Martius Rearrangement.[93, 94, 95]
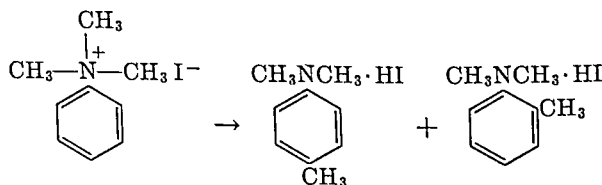
Some quaternary salts of phenolic Mannich bases, in which the amino group is present in an aniline derivative, rearrange readily in alkaline solution to form substituted benzylanilines.[66, 83, 96, 97]

[89a] Stevens and co-workers, *J. Chem. Soc.*, **1928**, 3193; **1930**, 2107, 2119; **1932**, 55, 1926, 1932; **1934**, 279.

[90] Campbell, Houston, and Kenyon, *J. Chem. Soc.*, **1947**, 93. Bock, Smith, and Auten, Atlantic City Meeting of the American Chemical Society, 1949, *Abstracts*, p. 70M.

[91] Dahn and Solms, *Helv. Chim. Acta*, 34, 907 (1951); Brewster and Kline, *J. Am. Chem. Soc.*, 74, 5179 (1952).

[91a] Kantor and Hauser, *J. Am. Chem. Soc.*, 73, 4122 (1951).

[92] Sommelet, *Compt. rend.*, 205, 56 (1937).

[93] Hickinbottom and Ryder, *J. Chem. Soc.*, **1931**, 1281.

[94] Hey, *J. Chem. Soc.*, **1931**, 1581.

[95] Wittig and Merkle, *Ber.*, 76, 109 (1943).

[96] Zincke and Hunke, *Ann.*, 349, 83 (1906); v. Auwers, *Ann.*, 334, 264 (1904).

[97] Corley and Blout, *J. Am. Chem. Soc.*, 69, 761 (1947).
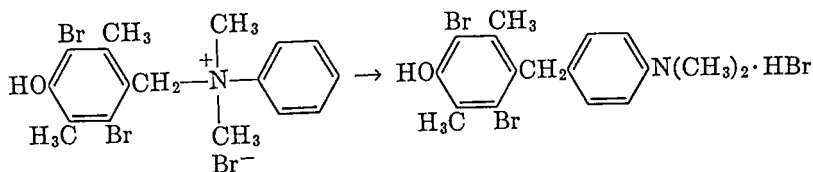
The Ladenburg Rearrangement.[98, 99]
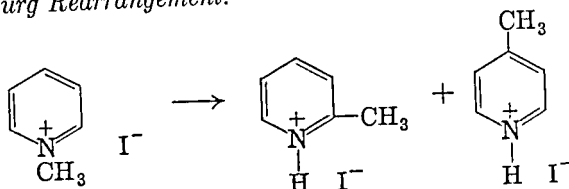
The Rearrangement of Diacylanilines.[100]
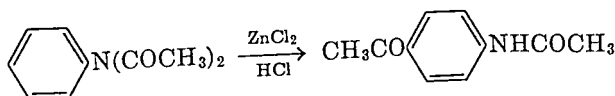
Reactions in Which the Carbon-Nitrogen Bond Broken Is One of the Bonds of a Heteroaromatic System. *The Reissert Reaction.*[101, 102]
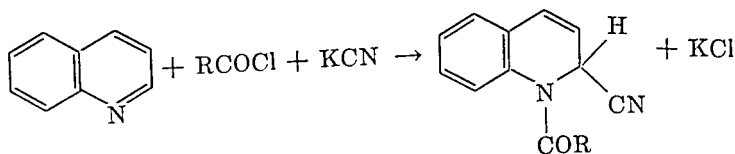
The products of this reaction (so-called Reissert compounds) are usually employed in the synthesis of aldehydes.
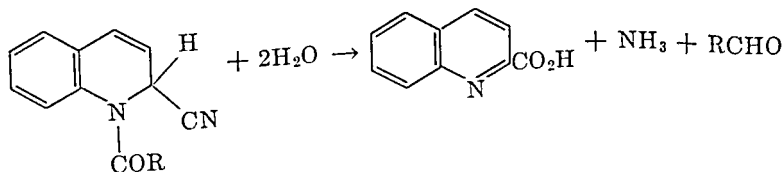
[93] Ladenburg, *Ber.*, **16**, 1410, 2057 (1883); *Ann.*, **247**, 1 (1888).

[99] Crook, *J. Am. Chem. Soc.*, **70**, 416 (1948).

[100] Chapman, *J. Chem. Soc.*, **127**, 2818 (1925).

[101] Reissert, *Ber.*, **38**, 1603 (1905); Sugasawa and Tsuda, *J. Pharm. Soc., Japan*, **56**, 103 (1936) [*C. A.*, **32**, 5836 (1938)]; Grosheintz and Fischer, *J. Am. Chem. Soc.*, **63**, 2021 (1941); Woodward, *ibid.*, **62**, 1626 (1940); McEwen and Hazlett, *ibid.*, **71**, 1949 (1949).

[102] Manske, *Chem. Revs.*, **30**, 113, 145 (1942).

The Reissert compounds may also be alkylated by Mannich bases.[102a]
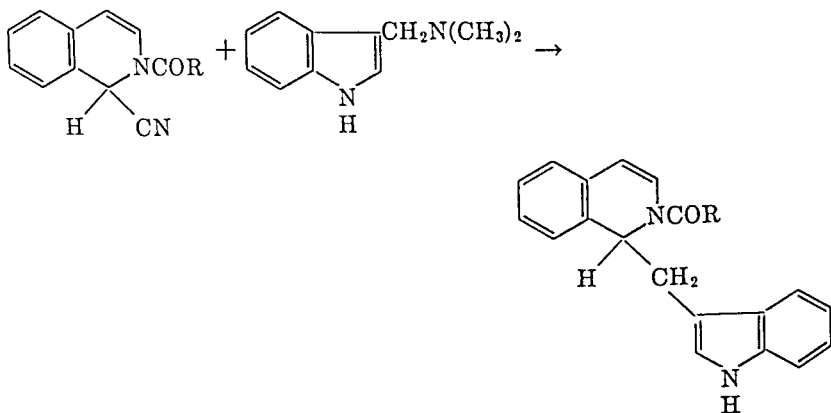
The Reaction of Alkali Cyanides with Alkylpyridinium Salts.[102, 103]
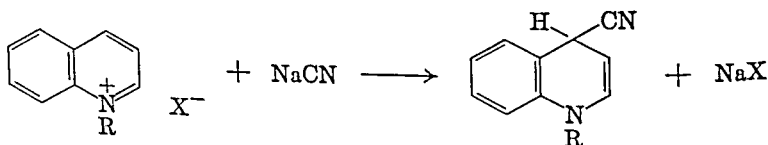
The Reaction of Nitro Compounds with Alkylpyridinium Salts.[104]
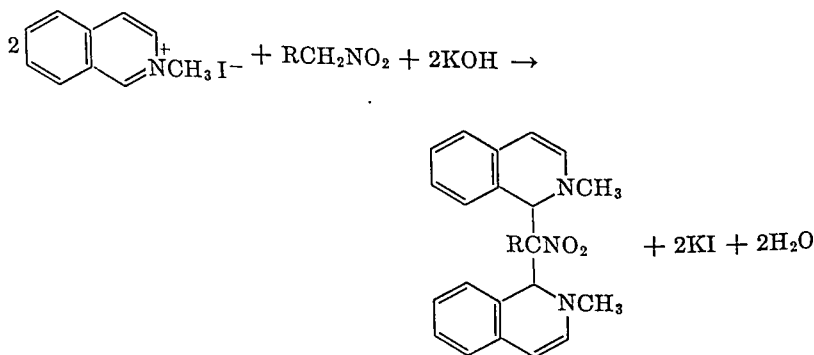
[102a] Boekelheide and Ainsworth, *J. Am. Chem. Soc.*, **72**, 2134 (1950).

[103] Kaufmann, *Ber.*, **51**, 116 (1918); Leonard and Foster, *J. Am. Chem. Soc.*, **74**, 2110, 3671 (1952).

[104] Leonard and Leubner, *J. Am. Chem. Soc.*, **71**, 3405 (1949); Leonard, Leubner, and Burk, *J. Org. Chem.*, **15**, 979 (1950); Leonard, DeWalt, and Leubner, *J. Am. Chem. Soc.*, **73**, 3325 (1951).

Nitrogen Alkylations

Amine Exchange Reactions of Quaternary Salts. When many quaternary ammonium salts, particularly those containing benzyl, allyl, or methyl groups, are heated with ammonia or with primary or secondary amines, an exchange of amino groups takes place.[10, 15, 16, 111, 112, 113]

$$\left[\begin{array}{c} R \\ | \\ R'—N—R \\ | \\ R \end{array} \right]^+ + HNR''_2 \rightarrow R'NR''_2 + NR_3 + H^+$$
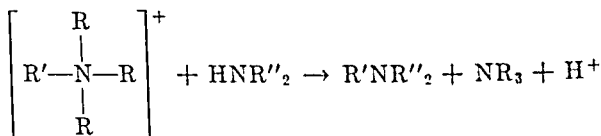
Amine Exchange Reactions of Mannich Bases. Simple amine exchange reactions have been observed with Mannich bases of nitroalkanes,[21a, 114] indole [41] (VII), phenols,[15a] and ketones,[67, 115] as well as with the benzaldehyde Mannich bases of β-naphthol [67] (LXIII).

$$C_6H_5CHN(CH_3)_2 \qquad\qquad C_6H_5CHNC_5H_{10}$$

LXIII

$$+ C_5H_{10}NH \rightarrow \qquad + NH(CH_3)_2$$
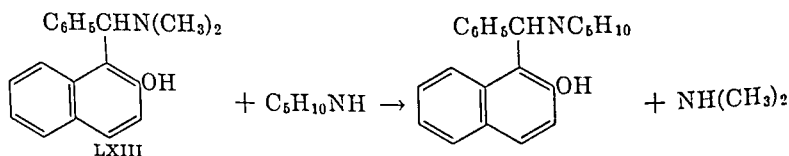
Quaternary salts of some Mannich bases (e.g., those of indole, VII, and those of acetophenone, XXV) react readily by amine exchange with tertiary amines (including Mannich bases) to give new quaternary salts. This reaction may be important as a side reaction in the quaternization of Mannich bases by means of such reagents as methyl iodide,[6b] for example, in the quaternization of gramine.

$$3 \qquad CH_2N(CH_3)_2 + 3CH_3I \rightarrow \qquad CH_2\overset{+}{N}(CH_3)_3 \quad I^-$$

VIIa

$$+ \qquad CH_2\overset{+}{N}CH_2 \qquad + \overset{+}{N}(CH_3)_4 \; I^-$$
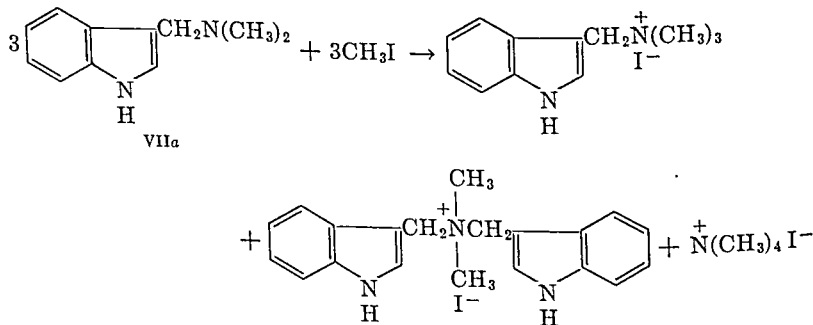
[111] Scholtz, *Ber.*, **24**, 2402 (1891); **31**, 414, 1700 (1898).
[112] v. Braun and co-workers, *Ann.*, **445**, 247 (1925); *Ber.*, **59**, 1786, 2330 (1926).
[113] Hultquist and co-workers, *J. Am. Chem. Soc.*, **70**, 23 (1948).
[114] Duden, Bock, and Reid, *Ber.*, **38**, 2036 (1905).
[115] Denton, Schedl, Neier, and Brookfield, *J. Am. Chem. Soc.*, **72**, 3792 (1950).

Compounds that do not permit amine elimination, such as α-dimethylaminomethyl-β-methoxynaphthalene[2] (IV, R = CH$_3$), β-dimethylaminopivalophenone[11] (XV), 1-methylgramine[75] (XXI), and 2-dimethylaminomethyl-2-nitropropane[21a] do not undergo an amine exchange reaction in the absence of added acid catalyst, such as hydrogen chloride or boron trifluoride.[75]

Formation of Pyrazolines from Ketonic Mannich Bases. The phenylhydrazones of ketonic Mannich bases form pyrazolines by internal amine exchange under conditions similar to those required for phenylhydrazone formation.[1, 116-120]
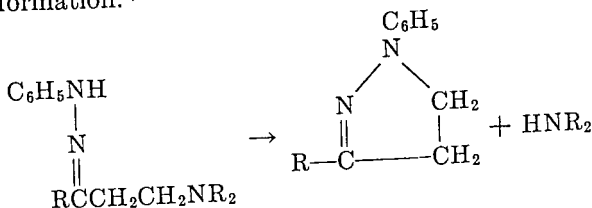
Conversion of Mannich Bases into Aldehydes. In an extension of the amine exchange reactions of Mannich bases, the base in acetic acid solution is allowed to react with hexamethylene tetramine.[121] The intermediate quaternary salt decomposes to yield an aldehyde.

$$RCH_2N(CH_3)_2 + (CH_2)_6N_4 + CH_3CO_2H \rightarrow$$

$$NH(CH_3)_2 + RCH_2N(CH_2)_6N_3^+ + CH_3CO_2^- \rightarrow RCHO$$
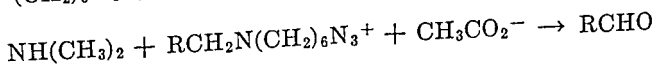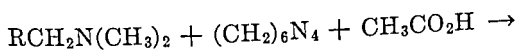
This process, which resembles the Sommelet reaction[122] for converting benzyl halides into aromatic aldehydes, has been applied successfully to the Mannich bases of indole, 2-phenylindole, 2-carbethoxyindole, and acetophenol, and β-naphthol, but has failed with Mannich bases of acetophenone, pyrrole, and 2-nitro-3-methylthiophene as well as 2-nitropropane. It was successful also with benzylamine and N-methylbenzylamine, but not with N,N-dimethylbenzylamine.

[116] Mannich and Bauroth, *Ber.*, **57**, 1108 (1924).
[117] Nisbet and Gray, *J. Chem. Soc.*, **1933**, 839.
[118] Levvy and Nisbet, *J. Chem. Soc.*, **1938**, 1053, 1572.
[119] Nisbet, *J. Chem. Soc.*, **1938**, 1237, 1568; **1945**, 126.
[120] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 14 (1939) [*C. A.*, **33**, 8196 (1939)].
[121] Snyder, Swaminathan, and Sims, *J. Am. Chem. Soc.*, **74**, 5110 (1952).
[122] Sommelet, *Compt. rend.*, **157**, 852 (1913); Angyal and co-workers, *J. Chem. Soc.*, **1949**, 2700, 2704; **1950**, 2141.

Oxygen Alkylations

Formation of Alcohols from Quaternary Ammonium Hydroxides.
Quaternary ammonium hydroxides, when heated strongly, may form
alcohols rather than olefins, particularly when benzyl, allyl, or, in some
cases, methyl groups are present and when no radicals, such as ethyl or
phenethyl, that lead to easy formation of olefins are present.[123-127]

$$R'\overset{+}{N}R_3 \, OH^- \rightarrow R'OH + NR_3$$
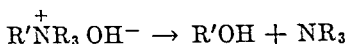
The formation of pseudobases from pyridinium hydroxides is formally
similar to the formation of alcohols from quaternary ammonium hy-
droxides.[128, 129]

Formation of Ethers from Quaternary Ammonium Phenoxides.[4, 130-136a]
Quaternary ammonium compounds have been used in the formation of
benzyl, methyl, ethyl, and allyl ethers of phenols.

Some of the quaternary ethoxides of p-nitroaniline and p-formylaniline
(p-aminobenzaldehyde) decompose to form alkoxy substituted ben-
zenes.[137]

Epoxides are formed in the Hofmann degradation of quaternary salts
of 1-hydroxy-2-amines.[138, 139, 140]

[123] Hofmann, *Ann.*, **78**, 253 (1851); **79**, 11 (1851); *Ber.*, **14**, 494 (1881).

[124] Ingold and Vass, *J. Chem. Soc.*, **1928**, 3125.

[125] von Braun, Teuffert, and Weissbach, *Ann.*, **472**, 121 (1929).

[126] Hanhart and Ingold, *J. Chem. Soc.*, **1927**, 997.

[127] von Braun, *Ann.*, **382**, 1 (1911).

[128] Decker, *Ber.*, **25**, 443 (1892).

[129] Hantzsch and Kalb, *Ber.*, **32**, 3109 (1899).

[130] Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926) [*C. A.*, **20**, 3695 (1926)].

[131] Henley and Turner, *J. Chem. Soc.*, **1931**, 1172.

[132] Griess, *Ber.*, **13**, 246 (1880).

[133] Boehringer, Ger. pat. 247,180 [*Frdl.*, **10**, 1215 (1912)].

[134] Rodionow, *Bull. soc. chim. France*, [4] **39**, 305 (1926).

[135] Rodionow, *Bull. soc. chim. France*, [4] **45**, 109 (1929).

[135] Tarbell and Vaughan, *J. Am. Chem. Soc.*, **65**, 231 (1943).

[135a] Kursanow, Setkina, and Rodionow, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, **1948**,
228 [*C. A.*, **42**, 4922 (1948)]; Kursanow and Setkina, *Doklady Akad. Nauk S.S.S.R.*, **65**,
847 (1949) [*C. A.*, **43**, 6622c (1949)]; Setkina and Kursanow, *Izvest. Akad. Nauk S.S.S.R.*,
Otdel. Khim. Nauk, **1949**, 311 [*C. A.*, **44**, 159a (1950)]; *ibid.*, **1951**, 81 [*C. A.*, **46**, 458
(1952)]; Setkina, *Izvest. Akad. Nauk S.S.S.R.*, Otdel. Khim. Nauk, **1950**, 216 [*C. A.*, **44**,
9337e (1950)].

[137] Zaki and Fahim, *J. Chem. Soc.*, **1942**, 270; Zaki and Tadros, *J. Chem. Soc.*, **1941**, 350.

[138] von Braun and Schirmacher, *Ber.*, **56**, 1845 (1923).

[139] von Braun, *Ber.*, **56**, 2178 (1923).

[140] von Braun and Münch, *Ber.*, **59**, 1941 (1926); Curtin, Harris, and Pollak, *J. Am.
Chem. Soc.*, **73**, 3453 (1951).

Formation of Esters from Quaternary Ammonium Salts of Carboxylic Acids.

Benzyl [4] and methyl [141] and ethyl [141a] esters of carboxylic acids have been prepared by heating the acids with quaternary ammonium hydroxides containing the appropriate radicals as the most readily replaced substituents on the nitrogen atom. Benzyl esters may also be obtained by heating methyl esters with benzyldimethylamine.[142]

Benzyldimethylamine reacts with acetic anhydride or benzoyl chloride to give benzyl acetate and benzoate respectively.[143] Phenolic Mannich bases similarly form acetyl derivatives of the corresponding methylolphenols.[14, 15a, 144, 145, 145a]

$$
\begin{array}{c}
\text{OH} \\
\bigcirc\text{CH}_2\text{N(CH}_3)_2 + 2(\text{CH}_3\text{CO})_2\text{O} \rightarrow
\end{array}
$$

$$
\begin{array}{c}
\text{OCOCH}_3 \\
\bigcirc\text{CH}_2\text{OCOCH}_3 + \text{CH}_3\text{CON(CH}_3)_2 + \text{CH}_3\text{CO}_2\text{H}
\end{array}
$$
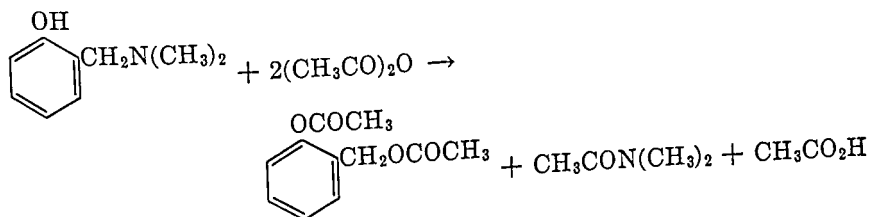
Sulfur Alkylations

Quaternary ammonium salts containing such anions as sulfide, hydrosulfide, mercaptide,[5, 146, 147] thiosulfate, thiocyanate, bisulfite, sulfite,[5, 147] and p-toluenesulfinate [4] decompose when heated to form alkyl derivatives of these anions containing carbon-sulfur bonds. Alkyl groups that can take part easily in these reactions are allyl,[147] benzyl,[5] and methyl,[146] in order of decreasing activity.

The ready cleavage of thiamin by bisulfite ion indicated the presence of a reactive benzyl type of quaternary ammonium group in the molecule.[148] Among tertiary amines, gramine (VIIa) has been used in the alkylation of sodium bisulfite.[148a] The Mannich bases of phenol will alkylate mercaptans.[148b] An extensive study of sulfur alkylations has been reported.[21b]

[141] Lawson and Collie, J. Chem. Soc., **53**, 624 (1888); Prelog and Piantanida, Z. physiol. Chem., **244**, 56 (1936); Fuson, Corse, and Horning, J. Am. Chem. Soc., **61**, 1290 (1939).

[141a] Kupferberg. J. prakt. Chem., [2] **16**, 440 (1877).

[142] Eliel and Anderson, J. Am. Chem. Soc., **74**, 547 (1952).

[143] Tiffeneau and Fuhrer, Bull. soc. chim. France, (4) **15**, 162 (1914).

[144] Madinaveitia, Anales soc. espan. fis. y quim., **19**, 259 (1921) [C. A., **16**, 1230 (1922)].

[145] Bruson and MacMullen, J. Am. Chem. Soc., **63**, 270 (1941).

[145a] For similar reactions, see Setkina and Kursanow, Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk, **1949**, 190 [C. A., **43**, 6161h (1949)].

[146] Clarke, J. Chem. Soc., **103**, 1689 (1913).

[147] Snyder and Speck, J. Am. Chem. Soc., **61**, 2895 (1939).

[148] Williams, Waterman, Keresztesy, and Buchman, J. Am. Chem. Soc., **57**, 536 (1935).

[148a] Wieland, Fischer, and Moewus, Ann., **561**, 47 (1948).

[148b] McCleary and Roberts, U. S. pat. 2,417,118 [C. A., **41**, 3819b (1947)].

Halogen Alkylations

Decomposition of Quaternary Ammonium Halides.   Quaternary ammonium halides decompose when heated to form alkyl halides and tertiary amines.[123]   Mixtures of amines and halides are often obtained

$$
\left[
\begin{array}{c}
R \\
| \\
R'\!-\!N\!-\!R \\
| \\
R
\end{array}
\right]^{+} X^{-} \rightarrow R'X + NR_3
$$
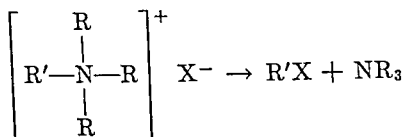
from mixed quaternary halides.[141, 149]   Allyl,[150] benzyl,[151, 152] and methyl [163] groups are lost as halides more readily than are other alkyl groups or the phenyl group.[127]   Quaternary ammonium halides containing an asymmetric nitrogen atom racemize readily in solution at room temperature.[154]

The von Braun Cyanogen Bromide Reaction.   Cyanogen bromide reacts with a tertiary amine to form a quaternary salt, which readily decomposes to form an alkyl halide and a dialkylcyanamide.[155, 156]

$$
\begin{array}{c}
R \\
| \\
R'N + BrCN \rightarrow \\
| \\
R
\end{array}
\left[
\begin{array}{c}
R \\
| \\
R'NCN \\
| \\
R
\end{array}
\right]^{+} Br^{-} \rightarrow R'Br +
\begin{array}{c}
R \\
| \\
NCN \\
| \\
R
\end{array}
$$
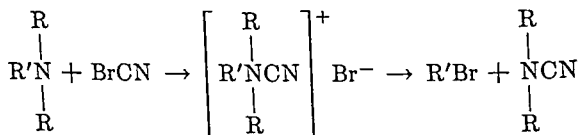
This reaction was extensively studied by von Braun.[157]   Its principal uses have been the degradation of alkaloids [158–162] and the cleavage of an alkyl group from N,N-dialkylanilines.[163, 164]   The von Braun cleavage is discussed in detail in Chapter 4.

[149] Collie and Schryver, *J. Chem. Soc.*, **57**, 767 (1890).

[150] Wedekind, *Ber.*, **35**, 766 (1902).

[151] Michler and Gradmann, *Ber.*, **10**, 2078 (1877).

[152] Marquardt, *Ber.*, **19**, 1027 (1886).

[153] Meyer and Lecco, *Ann.*, **180**, 173 (1876).

[154] Wedekind and Paschke, *Ber.*, **43**, 1303 (1910).

[155] von Braun, *Ber.*, **33**, 1438 (1900); Scholl and Norr, *ibid.*, **33**, 1550 (1900).

[156] Elderfield and Hageman, *J. Org. Chem.*, **14**, 605 (1949).

[157] von Braun and co-workers, *Ber.*, **33**, 2728, 2734 (1900); **35**, 1279 (1902); **40**, 3933 (1907); **41**, 2100, 2113 (1908); **42**, 2035, 2219 (1909); **43**, 1353, 3209 (1910); **44**, 1252, (1911); **47**, 3023 (1914); **51**, 96, 255 (1918); **55**, 3803 (1922); **56**, 1840, 2165 (1923); **63**, 2407 (1930); **70**, 1241 (1937); *Ann.*, **445**, 201 (1925); **449**, 249 (1926); **490**, 189 (1931); **507**, 1 (1933).

[158] Mossler, *Monatsh.*, **31**, 1 (1910).

[159] von Braun, *Ber.*, **47**, 2312 (1914); **49**, 2624 (1916).

[160] Speyer and Sarre, *Ber.*, **57**, 1427 (1924).

[161] Speyer and Rosenfeld, *Ber.*, **58**, 1125 (1925).

[162] Leuchs and Overberg, *Ber.*, **65**, 961 (1932); **66**, 79 (1933).

[163] von Braun, *Ber.*, **37**, 2670 (1904); **40**, 3914 (1907); **41**, 2165 (1908).

[164] Sachs and Weigert, *Ber.*, **40**, 4356 (1907).

Replacement of Amine by Hydrogen (Emde Reduction)

$$[RN(CH_3)_3]^+X^- + 2(H) \rightarrow RH + N(CH_3)_3 \cdot HX$$

$$RN(CH_3)_2 + H_2 \rightarrow RH + NH(CH_3)_2$$
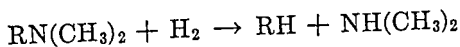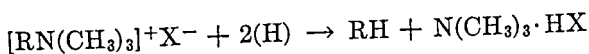
Quaternary salts may be reduced either by means of sodium amalgam (Emde reduction)[165–168] or lithium aluminum hydride,[168a] or catalytically;[169,170] tertiary amines are subject to catalytic reduction only.[15a,169–175] Many of these reductions are discussed in Chapter 5. Phenolic Mannich bases can also be reduced by means of sodium methoxide.[175a]

RELATED SYNTHETIC PROCESSES

Carbon-carbon alkylation by amine replacement is of particular value when a labile amino compound is more readily accessible as a starting material than is the corresponding halide or conjugated unsaturated compound. The following section is intended to place the reactions that have been discussed in perspective relative to other methods that result in the formation of similar products or are formally related to the amine replacement reactions. For obvious reasons, no attempt has been made to cover these aspects of synthetic organic chemistry in a detailed or exhaustive manner.

Carbon-Carbon Alkylations by Halogen Replacement

Some of the most familiar and important methods for the formation of carbon-carbon bonds involve replacement of the halogen atom of an

[165] Emde, *Ber.*, **42**, 2590 (1909).
[166] Emde and Kull, *Arch. Pharm.*, **272**, 469 (1934).
[167] Groenewoud and Robinson, *J. Chem. Soc.*, **1934**, 1692.
[168] von Braun and co-workers, *Ber.*, **49**, 501, 1283, 2613 (1916); **50**, 50 (1917); **55**, 3803 (1922); **56**, 1570 (1923).
[168a] Kenner and Murray, *J. Chem. Soc.*, **1950**, 406.
[169] Emde, *Helv. Chim. Acta*, **15**, 1330 (1932).
[170] Emde and Kull, *Arch. Pharm.*, **274**, 173 (1936).
[171] Birkofer, *Ber.*, **75**, 429 (1942).
[172] Baltzly and Buck, *J. Am. Chem. Soc.*, **65**, 1984 (1943); Baltzly and Russel, *J. Am. Chem. Soc.*, **72**, 3410 (1950).
[173] Caldwell and Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).
[174] Bachman and Levine, *J. Am. Chem. Soc.*, **69**, 2341 (1947).
[175] May and Mosettig, *J. Am. Chem. Soc.*, **70**, 686 (1948); Carlin and Landerl, *J. Am. Chem. Soc.*, **72**, 2762 (1950); Reeve and Sadle, *ibid.*, **72**, 3252 (1950); Karrman and Bladh, *Acta Chem. Scand.*, **4**, 1541 (1950) [*C. A.*, **45**, 7092 (1951)].
[175a] Cornforth, Cornforth, and Robinson, *J. Chem. Soc.*, **1942**, 682; Rapoport, King, and Lavigne, *J. Am. Chem. Soc.*, **73**, 2718 (1951).

alkyl halide.[176] Some of the more important of these methods are the following:

Friedel-Crafts Reaction.[177]
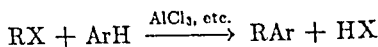
$$RX + ArH \xrightarrow{\text{AlCl}_3, \text{ etc.}} RAr + HX$$

Reaction with Organometallic Compounds.[178]

$$RX + MR' \rightarrow RR' + MX$$
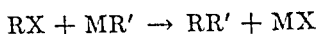
Alkylation of Active Methyl and Methylene Compounds.[179]

$$RX + Na\underset{Y}{\overset{Z}{-}C-}R' \rightarrow R\underset{Y}{\overset{Z}{-}C-}R' + NaX$$
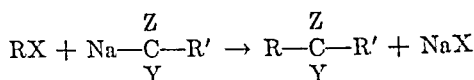
A particularly interesting example of this type of reaction represents a new route to cyclohexenones such as may be prepared by use of ketonic Mannich bases.[29]
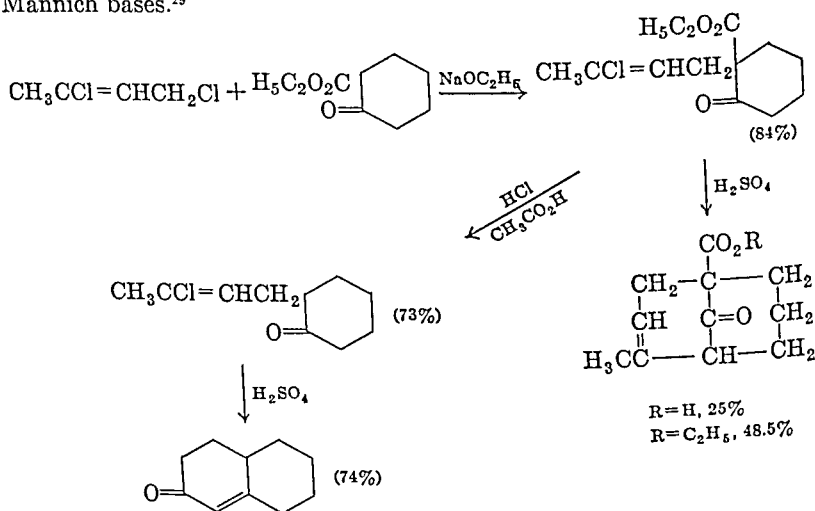
Replacement by Cyanide.[180]

$$RX + MCN \rightarrow RCN + MX$$
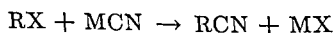
[176] Weygand, *Organic Preparations*, pp. 353–403, Interscience Publishers, New York, 1945.

[177] Price in Adams, *Organic Reactions*, Vol. III, p. 1, John Wiley & Sons, 1946.

[178] See Ref. 176, pp. 355–358.

[179] See Ref. 176, pp. 359–365.

[180] See Ref. 176, p. 367.

Carbon-Carbon Alkylations by Oxygen Replacement [181]

Friedel-Crafts Reaction.

$$ROR' + ArH \rightarrow R\text{---}Ar + HOR'$$
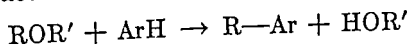
This reaction is not of general applicability.

Alkylations with Ethylene Oxide.

and/or
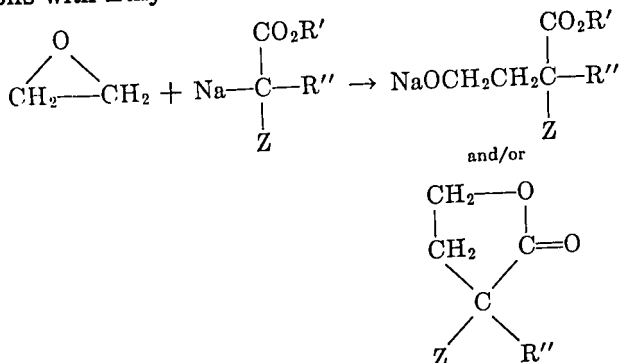
Alkylations with o-Hydroxybenzyl Alcohols.

(as well as *para* and crosslinked polymers)
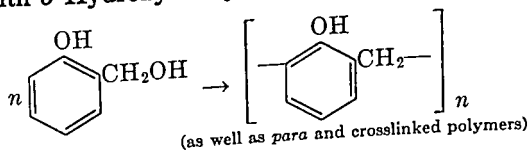
Alkylation with Diethyl Methoxymethylmalonate. [182, 183]

$$+ CH_3OCH_2CH(CO_2C_2H_5)_2 \rightarrow$$

$$+ CH_3OH$$
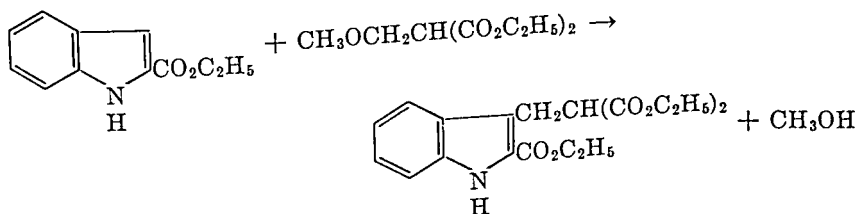
Carbon-Carbon Alkylations with Diazoacetic Ester. [184]

$$+ N_2CHCO_2C_2H_5 \rightarrow$$

$$+ N_2$$
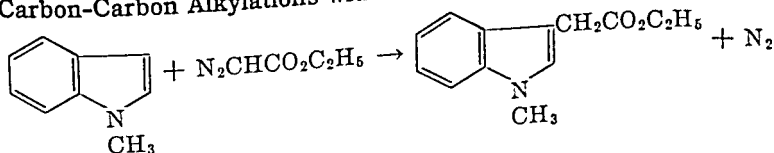
[181] See Ref. 176, pp. 404–414.
[182] Fischer and Nenitzescu, *Ann.*, **443**, 113 (1925).
[183] Maurer and Moser, *Z. physiol. Chem.*, **161**, 131 (1926).
[184] Piccini, *Gazz. chim. ital.*, **29**, 363 (1899).

Carbon-Carbon Alkylation by Sulfur Replacement [185]

$$\text{(thiopyranylium structure)} \quad + \quad \underset{O=}{\overset{CO_2C_2H_5}{\text{(cyclopentanone ester)}}} \quad \xrightarrow{\text{KOEt}} \quad \text{(product)}$$

with the dimethyl sulfonium iodide $\overset{+}{S}$, $\overset{|}{CH_3}$ I^- and the product containing $CH_2CO_2C_2H_5$, CH_2, CO, CH_2, CH_2, S, CH_3 groups and $O=$ cyclopentanone ring.
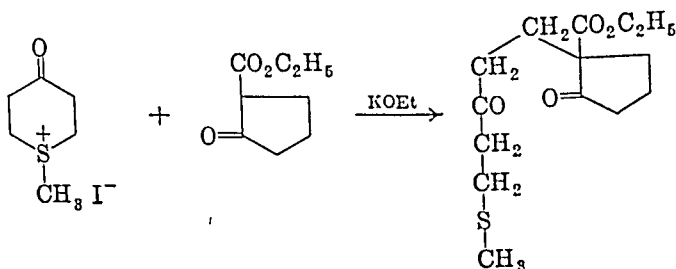
Coupling of Active Hydrogen Compounds by Condensation with Carbonyl Compounds

One-Step Condensations. *A. Formation of Symmetrical Products.*

$$AH + \underset{R}{\overset{R}{C}}{=}O + HA \rightarrow A{-}\underset{R}{\overset{R}{C}}{-}A + H_2O$$
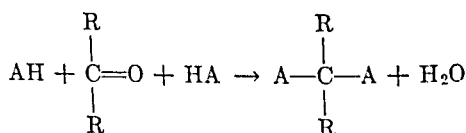
This process is useful in the formation of symmetrical compounds, except that it cannot be used when the hydrogen in H—A and the α-hydrogens in RCOR are of comparable activity. Phenols, malonic esters, β-keto esters, α-cyano esters and secondary amines are among the types of compounds that will undergo symmetrical coupling of the type shown above. A familiar example is the synthesis of DDT.

$$Cl{-}\langle\text{C}_6\text{H}_4\rangle + \underset{CCl_3}{\overset{H}{C}}{=}O + \langle\text{C}_6\text{H}_4\rangle{-}Cl \rightarrow Cl{-}\langle\text{C}_6\text{H}_4\rangle CH\langle\text{C}_6\text{H}_4\rangle{-}Cl + H_2O$$

with CCl_3 on the central carbon.
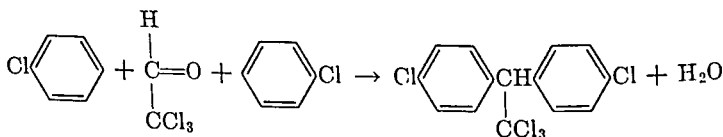
B. Formation of Unsymmetrical Products.

$$AH + \underset{R}{\overset{R}{C}}{=}O + HB \rightarrow A{-}\underset{R}{\overset{R}{C}}{-}B + H_2O$$
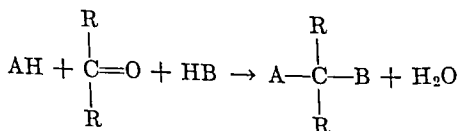
When the active hydrogen compounds to be coupled are markedly different in structure and activity, good yields of unsymmetrical products

[185] Cardwell, *J. Chem. Soc.*, **1949**, 715.

may be obtained.   The halo-alkylation [186] and amino-alkylation (Mannich) reactions [1] (p. 103) of active hydrogen compounds are well-known examples of unsymmetrical coupling reactions.   The reaction of N-methylolamides with aromatic compounds [6,187] is a less familiar example.

$$C_6H_5CONH_2 + CH_2O \rightarrow C_6H_5CONHCH_2OH$$

$$C_6H_5CONHCH_2OH +$$
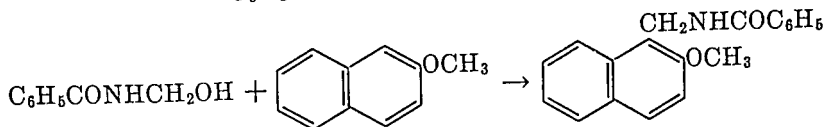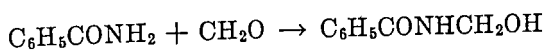
The cyanomethylation of indole [188,189] is one of the few examples in which two different carbanion-forming substances can be coupled by means of formaldehyde to yield unsymmetrical products.

Two-Step Condensation-Addition Reactions.   The first step in reactions of this type is the familiar Perkin-Claisen-Knoevenagel reaction; [190,191] the second step consists in addition of an active hydrogen compound to a conjugated unsaturated system (Michael reaction).[192] An example is the synthesis of phenylsuccinic acid.[193]

$$C_6H_5CHO + CH_2(CN)CO_2H \rightarrow$$
$$C_6H_5CH{=}C(CN)CO_2H \xrightarrow{C_2H_5OH} C_6H_5CH{=}C(CN)CO_2C_2H_5$$

$$C_6H_5CH{=}C(CN)CO_2C_2H_5 + HCN \rightarrow$$
$$C_6H_5CHCHCO_2C_2H_5 \xrightarrow[\text{and decarboxylation}]{\text{Hydrolysis}} C_6H_5CHCH_2CO_2H$$
$$\underset{NC \quad CN}{| \quad |} \qquad\qquad \underset{CO_2H}{|}$$
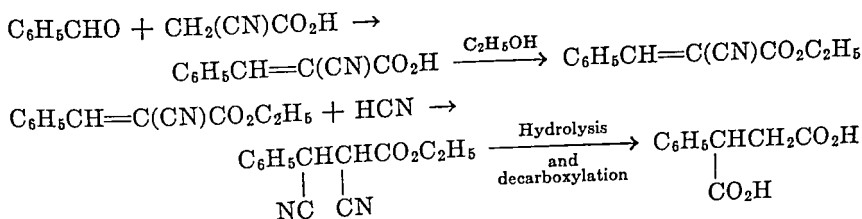
This process can be employed to advantage when the conjugated unsaturated compound is easily prepared and stable enough to be isolated and purified, and it is of principal value when the carbonyl compound which serves as a coupling agent is some material other than formaldehyde.   In many syntheses, an active hydrogen compound can be added to a conjugated unsaturated compound, such as acrolein or acrylonitrile,[194] which is more easily prepared in some other way.   In

[186] Fuson and McKeever in Adams, *Organic Reactions*, Vol. I, p. 63, John Wiley & Sons, 1942.

[187] Einhorn, *Ann.*, **343**, 207 (1905); **361**, 113 (1908); Downes and Lions, *J. Am. Chem. Soc.*, **72**, 3053 (1950).

[188] Bauer and Andersag, U. S. pat. 2,222,344 [*C. A.*, **35**, 1807 (1941)].

[189] Sankyo, Jap. pat. 161,544 [*C. A.*, **43**, 2236 (1949)].

[190] See Ref. 176, pp. 418–438.

[191] Johnson in Adams, *Organic Reactions*, Vol. I, p. 210, John Wiley & Sons, 1942.

[192] Allen and Blatt in Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. I, pp. 672–688, John Wiley & Sons, New York, 1944.

[193] Lapworth and Baker, *Org. Syntheses Coll. Vol.* **1**, 181, 451 (1941).

[194] Bruson in Adams, *Organic Reactions*, Vol. V, p. 79, John Wiley & Sons, 1949.

such syntheses the relationship of synthetic methods is only formal, though the products obtained are structurally similar to those formed by the two-step condensation-addition process outlined above.

CHOICE OF EXPERIMENTAL CONDITIONS

Choice of Reactants

Carbon-carbon alkylations of hydrogen cyanide and active methyl or methylene compounds by Mannich bases are part of a two-step process for coupling active hydrogen compounds by means of formaldehyde with the loss of water. It is often theoretically possible to form ZCH_2Z'

$$ZH + CH_2O + HN(R)_2 \rightarrow ZCH_2N(R)_2 + H_2O$$

$$ZCH_2N(R)_2 + HZ' \rightarrow ZCH_2Z' + HN(R)_2$$
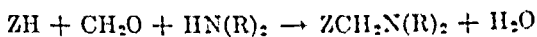
by alkylation of ZH with the Mannich base of HZ'. It is apparent, then, that it may at times be necessary to decide which active hydrogen compound should be converted to its Mannich base and which should be reserved as the compound to be alkylated if best yields are to be obtained.

If the formation of γ-ketonitriles and aryl- or indole-acetonitriles or acetic acids is desired, there seems to be no alternative to the use of ketonic, phenolic, or indole Mannich bases. At any rate, the use of α-aminoacetonitriles as alkylating agents is seldom feasible.[59a,c] However, when the desired process is the coupling of two active hydrogen compounds, neither of which is hydrogen cyanide, there is often a choice of which one to employ as a Mannich base and which as the reagent to be alkylated.

The following points should be considered.

1. The Mannich reaction takes place readily with compounds containing even only moderately active methyl or methylene groups.

2. Only compounds containing highly active methylene groups are easily alkylated by means of Mannich bases. Compounds that contain only moderately active methylene groups, such as simple ketones, usually require the presence of strong bases such as sodium amide capable of converting them to enolates if they are to be alkylated by Mannich bases.

3. Only those tertiary amines that can form conjugated unsaturated systems by amine elimination are suitable for use as alkylating agents (p. 126).

4. Only those quaternary ammonium salts that can suffer amine elimination or that possess allylic systems are suitable for use as alkylating agents (p. 104).

In the cases under consideration, then, it is desirable to convert to its Mannich base the active methyl or methylene compound possessing the least acidic hydrogen atoms, provided, of course, that this Mannich base can undergo amine elimination or possesses an allylic system; and to use the appropriate active methylene compound possessing the most acidic hydrogen atom (only one such active hydrogen atom is necessary) as the reagent to be alkylated.

Mannich bases that can suffer amine elimination possess active hydrogen atoms and could, conceivably, be subject to alkylation. Intermolecular self-alkylation of the Mannich base (p. 103) should be most prominent in alkylations of compounds containing hydrogen atoms whose acidity is similar to or less than that of the active hydrogen atoms of the Mannich base. It is probable that this accounts for the facts that phenolic Mannich bases give only diarylmethanes in attempted base-catalyzed alkylations of active methylene compounds, and large amounts of diarylmethanes in their reactions with hydrogen cyanide, and that low yields of the desired alkylation product are usually obtained when ketones are alkylated by quaternary salts of ketonic Mannich bases. In the latter case, formylation of the ketone prior to alkylation may result in an improved yield (p. 114).[30a]

advantages, since their quaternary salts are often more soluble in inert solvents than the corresponding halides.

Ease of Purification of the Mannich Bases or Their Salts. Many of the simpler Mannich bases of ketones may be purified by distillation; high temperatures are to be avoided, because amine elimination may occur. It is advantageous to use the relatively low-boiling dimethyl-amino Mannich bases.

Ketonic Mannich bases are best stored as their hydrochlorides, in which form they are usually isolated. Dimethylamino, piperidino, and· morpholino Mannich base hydrochlorides are particularly easily crystallized. The dimethylamino and morpholino Mannich base hydrochlorides are often appreciably more hygroscopic than the piperidine derivatives.

The piperidino and morpholino Mannich bases of phenols are generally crystalline and stable, whereas a number of the dimethylamino, diethyl-amino and, especially, dibutylamino Mannich bases of phenols are thick liquids which are not always distillable. Most of the Mannich bases of indole are crystalline and stable.

Quaternary salts of Mannich bases are often too unstable to permit long storage. Indeed, quaternary salts of some phenolic Mannich bases decompose at room temperature or lower at rates that preclude their isolation. Wilds and Shunk [26] have shown the necessity of using pure quaternary salts of ketonic Mannich bases in alkylations of active methylene compounds if good yields of pure products are to be obtained. Piperidino, dimethylamino, and, especially, morpholino Mannich bases form easily crystallizable quaternary salts.

Inertness of the Amine Undergoing Replacement. Derivatives of aniline would generally be expected to be unsuitable for use in carbon-carbon alkylations by amine replacement because of the ease with which nuclear substitution in the aromatic amine could occur.

Volatility of the Amine Undergoing Replacement. The elimination of amines from Mannich bases is reversible.[67, 109] If the secondary amine formed during the reaction is not removed, it could compete for the conjugated unsaturated compound with the substance to be alkylated. As quaternary salts of Mannich bases can undergo facile amine exchange reactions with tertiary amines,[6b, c, 8a] amine elimination from such salts is probably reversible too, and removal of the tertiary amine by volatilization would seem to be desirable also. Trimethylamine (b.p. 3.5°), dimethylamine (b.p. 7.4°) and diethylamine (b.p. 55°) are readily distilled from the reaction mixture during the reaction when the solvent· is, for example, ethanol. Piperidine (b.p. 106°) and morpholine (b.p. 126–130°) could be removed in this manner only when higher boiling

solvents, such as hexanol, toluene, xylene, dibutyl ether, or Diethyl Carbitol, are used. One of the most convenient methods for following the course of an amine replacement reaction is observation of the evolution of a volatile amine.

Choice of Solvents, Operating Temperatures, etc.

The choice of solvents, reaction temperatures, reaction times, and apparatus to be used in amine replacement reactions varies according to the nature of the reaction and will be considered in more detail in the following sections. A few general remarks can be made at this point, however.

Mannich bases and their salts seem to be sensitive to air oxidation in alkaline reaction media and at temperatures required for some of the reactions. Although it is not invariably necessary to employ an inert atmosphere, such as nitrogen, in these reactions, it would seem to be generally desirable. A slow nitrogen stream also serves to sweep volatile amines out of the reaction mixture, thus making it somewhat easier to follow the reaction, which may be assumed to be completed when amine evolution (detected by odor or by moist red litmus paper) ceases.

Experimental Conditions for Particular Types of Carbon-Carbon Alkylations

Replacement of Amino Groups by Cyanide. *Use of Ketonic Mannich Bases.* The method of Knott [13] seems to be generally applicable for the formation of γ-ketonitriles from the hydrochlorides of dimethylamino Mannich bases of aryl methyl ketones (see preparation of β-benzoyl-propionitrile, LXIV, p. 155) and requires no comment. It is possible that modifications in this procedure may be required if other types of Mannich bases are employed.

$$C_6H_5COCH_2CH_2CN$$
LXIV
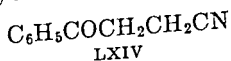
Use of Mannich Bases of Indoles and Phenols. A solution of the Mannich base and an excess (100–500%) of sodium cyanide in aqueous ethanol is heated under nitrogen with reflux until the evolution of secondary amine and ammonia is complete or greatly reduced (36–80 hours) (*Hood*). The indole- or aryl-acetic acid formed may be contaminated with the corresponding acetamide, and, when phenolic Mannich bases are used, with diarylmethanes or phenol-formaldehyde resins. The diarylmethanes and phenol-formaldehyde resins are generally insoluble in sodium carbonate; their removal is illustrated in the

preparation of 3-indoleacetic acid, p. 155, and 2-hydroxy-1-naphthalene-acetic acid, p. 156.

The conversion of Mannich bases of phenols and indoles to nitriles by reaction with hydrogen cyanide in benzene at 150° in an autoclave has been described only in the patent literature.[17]

Use of Quaternary Salts of Benzylamines. The use of these salts is of little synthetic importance in the benzene series since the corresponding benzyl chlorides are often easily prepared by chloromethylation.[148] The quaternary salts of furfurylamines (XII, R = H) and especially 5-methylfurfurylamines (XII, R = CH₃) may prove useful, for the amines are more easily prepared and handled than the corresponding halides and may give rise to different products (p. 107).

The method consists in either distilling an aqueous solution of the quaternary salt and alkali cyanide at atmospheric pressure to remove all the water or simply mixing the dry quaternary salt with dry sodium cyanide and then carefully heating the residue or mixture in vacuum to a temperature of 150–200° so that the nitrile distils as it is formed. Over-heating should be avoided, since the reaction may become quite violent. The nitrile is usually contaminated with the tertiary amine corresponding to the quaternary salt. In another modification of the technique, an aqueous paste of the quaternary salt and the cyanide is heated to about 200°, and the nitrile formed is swept out with superheated steam at the same temperature.[10]

Alkylation of Active Methyl and Methylene Compounds

Although conditions for the alkylation of active methyl and methylene compounds by means of Mannich bases are in general similar, rather wide variations in procedure have been employed. The following generalizations can be made, however.

An inert atmosphere is generally employed; apparently Mannich bases or intermediates in the alkylation reactions (such as vinyl ketones) are sensitive to oxygen, yielding tars or colored products as a result of oxidation or free-radical catalyzed polymerization.

As previously pointed out, ionization of the compound to be alkylated is necessary if the reaction is to occur. This ionization may be caused by the basic character of the Mannich base itself (as in alkylations of ethyl nitroacetate[19] or tricarbethoxymethane[17]) or by added sodium hydroxide, sodium ethoxide (as in alkylations of derivatives of malonic ester or of β-keto esters), or sodium amide (as in alkylations of ketones). It seems best to use a base that is no stronger than necessary, if multiple alkylations and other condensation reactions are to be avoided.

Only catalytic amounts of added base are required when Mannich bases are employed as alkylating agents; the base may be added to a mixture of the Mannich base and the substance to be alkylated. Alkylations under these conditions are often very slow. Some alkylations proceed just as well or even better in the absence of base.[21b]

When quaternary ammonium salts are the alkylating agents, an equivalent amount of base is necessary since it is consumed during the reaction. In practice, the sodium enolate of the active methylene compound is first formed, and the quaternary salt is then added to the reaction mixture. Alternatively, a quaternizing agent such as methyl iodide can be added to a mixture of the Mannich base and the sodium enolate of the active methylene compound to be alkylated. Alkylations of this type have only rarely been carried out without solvent; occasionally an excess of the active methylene compound to be alkylated is the solvent. It is obvious that solvents possessing hydrogen atoms more acidic than those of the substance to be alkylated are unsuitable for these reactions, since they would destroy the enolate. Thus, except in alkylations of such strongly acidic substances as diethyl cyanomalonate, water seems to have a deleterious effect (see, however, ref. 213). Absolute ethanol has been widely used as a solvent in alkylations of malonic esters and β-keto esters. The sodium enolates of ketones are generally formed by reaction with sodium amide in ether, pyridine, or benzene; and the quaternary salt alkylating agent, suspended in the same solvents or dissolved in an alcohol, is then added. In the alkylation of 1-methyl-5-methoxy-2-tetralone (LXV) with diethylaminobutanone [35] (p. 160), potassium ethoxide was satisfactory as a condensing agent; in this

LXV
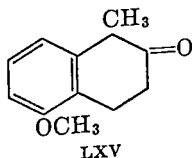
instance the methiodide of the Mannich base (formed on the walls of the reaction vessel) and a benzene solution of the ketone were brought together first and the base was then added in ethanolic solution. This technique gave an unusually high yield (71%) of the alkylation product. In alkylations of malonic ester derivatives by gramine (VIIa) (in the presence of powdered sodium hydroxide), toluene or xylene (which dissolve both reactants) has been used successfully. Polyfunctional high-boiling ethers, such as Diethyl Carbitol, are good solvents for the sodio derivatives of active methylene compounds and seem to dissolve

appreciable amounts of some quaternary ammonium salts; such ethers may prove to be useful solvents in alkylations of sodium enolates of active methylene compounds by means of quaternary salts.

EXPERIMENTAL PROCEDURES

The formulas of certain of the substances described in the following preparations are given herewith for purposes of reference.

$CH_2CHCH_2CH_3$
NO_2
LXVI

=O
$CH_2CH_2NO_2$
LXVII

OH
=O
$CO_2C_2H_5$
LXVIII

=O
CO_2H
LXIX

=O
LXX

CO_2CH_3
$-CH_2CH_2COCH_3$
O
LXXI

CO_2CH_3
O
LXXII

CO_2CH_3
=O
LXXIII

=O
LXXIV

=O
CH_3
LXXV

LXXVI

LXXVII

LXXVIII
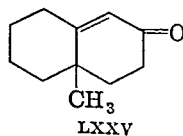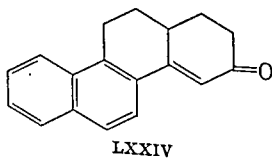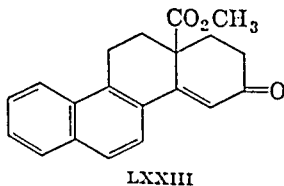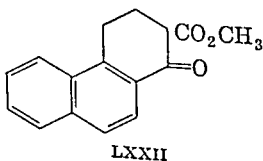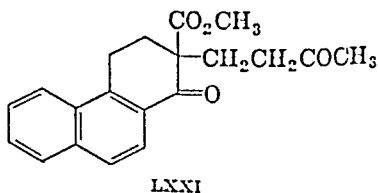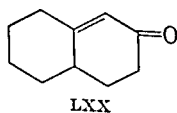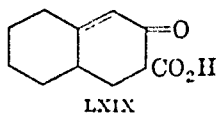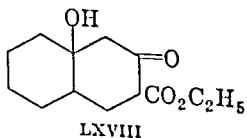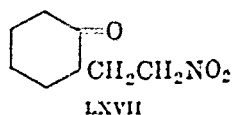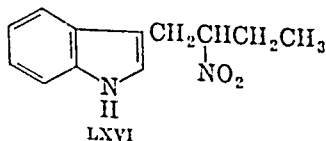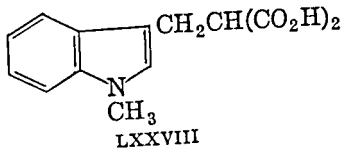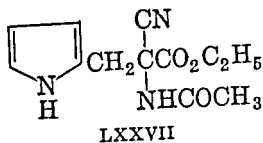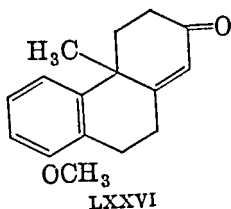
β-Benzoylpropionitrile (LXIV).[13]* To a mixture of 213.5 g. (1.0 mole) of β-dimethylaminopropiophenone hydrochloride[195] (XXV, R = CH₃) and 130 g. (2.0 moles) of potassium cyanide in a 5-l. flask is added 2.6 l. of boiling water. The mixture, consisting of an aqueous and an oily layer, is heated under reflux for thirty minutes. Part of the dimethyl-amine which is evolved distils and may be collected in dilute hydrochloric acid. When the mixture is chilled, the oil solidifies and crystals sepaa-rate from the water layer. β-Benzoylpropionitrile (105 g., 67%) is separated by filtration and is crystallized from a benzene-light petroleum mixture, forming almost colorless blades, m.p. 76°.

3-Indoleacetic Acid (XX) and 3-Indoleacetamide.[16]* A mixture of 25.0 g. (0.144 mole) of gramine (3-dimethylaminomethylindole, VIIa),[196] 35.2 g. (0.717 mole) of sodium cyanide, 280 ml. of 95% ethanol, and 70 ml. of water is boiled under reflux for eighty hours. To the cooled reaction mixture is added 350 ml. of water. The solution is treated with Norit, filtered, concentrated under reduced pressure until all the ethanol has been removed, cooled to 5°, and filtered. The solid on the funnel is recrystallized from ethanol and ether to give 5.0 g. (20%) of 3-indoleacetamide, m.p. 149–151°.

The reaction mixture, after removal of the amide by filtration, is concentrated under reduced pressure to a volume of about 300 ml. and cooled to 10°. Dropwise addition of cold, concentrated hydrochloric acid (*Hood!*) to the vigorously stirred solution causes precipitation of crude, slightly pink 3-indoleacetic acid. The crude material is filtered and dried at 70°; yield, 20.0 g. (79%) of material melting at 158–161°.

* Because an alkali cyanide is used, this preparation should be run in a well-ventilated hood. The waste liquors must be handled and disposed of with care, since they contain considerable amounts of cyanide.

[195] Maxwell, *Org. Syntheses*, **23**, 30 (1943).

[196] Kühn and Stein, *Ber.*, **70**, 567 (1937).

The crude product can be recrystallized from ethylene dichloride containing a small amount of ethanol to give 17.4 g. (69%) of pure 3-indoleacetic acid, melting at 167–168°.

A solution of 1.0 g. of 3-indoleacetamide, 1.2 g. of sodium hydroxide, and 8 ml. of water is boiled for four hours. The cooled solution (5°) is treated with Norit, filtered, and made strongly acid (about pH 1.5) with concentrated hydrochloric acid. The acid which precipitates is collected by filtration and dried at 70°. The yield of 3-indoleacetic acid melting at 167–168° is 0.95 g. (95%). The over-all yield of 3-indoleacetic acid from gramine is 88%.

2-Hydroxy-1-naphthaleneacetic Acid (XVIII).[15]* A solution of 4.2 g. (0.02 mole) of 1-dimethylaminomethyl-2-hydroxynaphthalene [197,198] (IV, R = H) and 2.09 g. (0.04 mole) of sodium cyanide in 60 ml. of 50% ethanol is heated under reflux in a nitrogen atmosphere for thirty-six hours, at the end of which time the evolution of dimethylamine and ammonia is complete. The flask is cooled to room temperature under a slow stream of nitrogen, and the yellow solution is poured without delay into 100 ml. of water. Dry Ice (100 g.) is added to the solution in small portions (hydrogen cyanide is evolved in this process). The white precipitate which forms when the solution is saturated with carbon dioxide is removed by filtration and washed with water. This material is crude di-(2-hydroxy-1-naphthyl)methane (XIX).

To the filtrate is added 50 g. of ice, and then slowly and with stirring, under a good hood, 50 ml. of concentrated hydrochloric acid, whereupon glistening platelets of 2-hydroxy-1-naphthaleneacetic acid separate. This material is collected by filtration, washed with 10% hydrochloric acid and then with water. There is obtained 1.90 g. (47%) of air-dried product melting at 146.5°. Often the material has a steel-blue color; the color can be removed by dissolving the acid in aqueous sodium carbonate, filtering, and reprecipitating with acid.

1-β-Indolyl-2-nitrobutane (LXVI).[18] A mixture of 10 g. (0.058 mole) of gramine [196] (VIIa), 50 ml. of redistilled 1-nitropropane, and 2.6 g. of solid sodium hydroxide is heated under reflux for six to eight hours or until amine evolution ceases. The solution is cooled and acidified with 50 ml. of 10% aqueous acetic acid and is then diluted with 200 ml. of ether. It is then washed with four 75-ml. portions of water, shaken with Norit, and filtered. The solvents are distilled at room temperature under

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* Because an alkali cyanide is used, this preparation should be run in a well-ventilated hood. The waste liquors must be handled and disposed of with care, since they contain considerable amounts of cyanide.

[197] Décombe, *Compt. rend.*, **197**, 258 (1933).

[198] Ger. pat. 89,979 [*Frdl.*, **4**, 98 (1899)].

vacuum, leaving a viscous oil. Distillation of the oil at 157°/0.2 mm. furnishes 10.6–11.9 g. (82–95%) of 1-β-indolyl-2-nitrobutane, m.p. 90–91°.

Ethyl Skatylnitroacetate (XXIII).[19]   In a 250-ml. flask, fitted with a stirrer, a thermometer, a nitrogen inlet, and a condenser, is placed 8.66 g. (0.05 mole) of gramine [196] (VIIa), 13.3 g. (0.10 mole) of ethyl nitro-acetate,[199,200] and 50 ml. of dry xylene. A slow stream of nitrogen is passed through the vigorously stirred mixture, and the temperature is raised to 90–100° and held there for five hours. (About one-half the calculated amount of dimethylamine may be collected in a trap through which the exit gases pass.) The hot solution is filtered, and the xylene is distilled under reduced pressure. The residual gum is taken up in chloroform, and the solution is extracted with two 50-ml. portions of 10% hydrochloric acid solution and then washed with water until neutral. The chloroform solution is dried over magnesium sulfate, the chloroform is removed by distillation at 20–30 mm. and the excess ethyl nitroacetate is distilled at 1 mm. The oil that remains is dissolved in chloroform, and the solution is extracted with successive portions of 5% sodium hydroxide solution until the oil that separates on acidification of a test portion is negligible in amount. The combined basic extracts are acidified with 10% hydrochloric acid, the temperature of the mixture being kept below 20°, and then extracted with chloroform. The chloroform solution is dried and concentrated; the residual oil crystallizes readily. The yield of ethyl skatylnitroacetate is 11.8 g. (90%). The melting point of a sample recrystallized from benzene-petroleum ether is 62.0–62.8°.

2-(2′-Nitroethyl)cyclohexanone (LXVII).[21]   A mixture of 15 g. (0.097 mole) of 2-dimethylaminomethylcyclohexanone [201] (XVI) and 9.2 g. (0.151 mole) of nitromethane is heated on a steam bath; 27 ml. of a 10% solution of sodium methoxide in methanol is added in one portion with vigorous stirring. As soon as the reaction product becomes solid, the solution is diluted with 20 ml. of methanol and stirred without further heating until the evolution of dimethylamine is complete. The sodium salt of the product is dissolved in water; the solution is cooled in an ice-salt bath and acidified with acetic acid. The red-brown oil that separates is taken up in several portions of ether, and the combined ethereal solutions are washed with water and dried over sodium sulfate. The ether is distilled, and the residual oil (12 g., 72%) is distilled at 160°/14 mm. for purification.

[199] Steinkopf, *Ber.*, **42**, 3925 (1909); *Ann.*, **434**, 21 (1923).
[200] Feuer, Hass, and Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).
[201] Mannich and Braun, *Ber.*, **53**, 1874 (1920).

2-Keto-3-carbethoxy-9-hydroxydecalin (LXVIII).[24]   A mixture of 16 g. of 2-dimethylaminomethylcyclohexanone [201] (XVI) and 15 g. of ethyl acetoacetate is treated on the first, third, fifth, and seventh days of standing with a solution of 0.1 g. of sodium in 3 ml. of absolute ethanol. The solution turns yellow, then red. After fourteen days the reaction is complete. (Further addition of sodium ethoxide only lowers the yield; it is not advantageous to add the alkoxide in one portion.) After the first four or five days of standing, crystals form in the solution and rapidly increase in bulk. The crystal mass is filtered from the green fluorescent liquid and washed with dilute hydrochloric acid and a little water. After recrystallization from ethanol and drying, the fine white needles weigh 18 g. (73%) and melt at 146°.

2-Keto-3-carboxy-Δ^{1,9}-octalin (LXIX).[24]   Six grams of the ethyl ester LXVIII and 1.7 g. of potassium hydroxide are dissolved in 40 ml. of cold water. The solution is allowed to stand four days and is then treated with sulfuric acid until acid to Congo Red; a powdery mass precipitates. The aromatic odor of this material is probably due to the presence of 2-keto-Δ^{1,9}-octalin (LXX). The acid is best purified by dissolving it in cold sodium carbonate solution and reprecipitating with hydrochloric acid. The material is obtained in good yield and melts at 95° with liquefaction and loss of carbon dioxide.

2-Keto-Δ^{1,9}-octalin (LXX).[24]   When the keto acid LXIX is melted, 2-keto-Δ^{1,9}-octalin boiling at 140–141°/14 mm. is formed in yields of about 75%.

2-γ-Ketobutyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene (LXXI).[26]   The sodium enolate of 2-carbomethoxy-1-ketotetrahydrophenanthrene [202] (LXXII) is prepared by heating 2.07 g. of the keto ester with a solution of 0.19 g. of sodium in 10 ml. of dry thiophene-free benzene. The mixture, containing the insoluble sodium salt, is then cooled in an ice bath, and the methiodide from 2.5 g. of redistilled 1-diethylamino-3-butanone [26] (XXIV, R = C$_2$H$_5$) is added in 10 ml. of methanol. The sodium salt slowly dissolves, and, after four hours at room temperature, another crystalline precipitate separates.   The mixture is refluxed for one hour. The clear solution is then diluted with water and extracted twice with benzene. After the solution has been washed with water, dilute acid, and water, the benzene is evaporated and the residue is crystallized from ethyl acetate to give 2.31 g. of cubic prisms, m.p. 141–143°. A second crop (0.18 g., m.p. 130–140°) is a mixture of prisms and needles which can be separated by adding petroleum ether, suspending the lighter needles by swirling, and decanting

[202] Bachmann and Wilds, *J. Am. Chem. Soc.*, **62**, 2084 (1940).

them with the liquid. Recrystallization of the residue affords 0.12 g. more of the prisms, m.p. 139–142°, making the total yield 92%. When further purified by distillation at 0.5 mm. and recrystallization from ethyl acetate, the material melts at 145–145.3°.

Cyclization of the Tricyclic Keto Ester LXXI to the Tetracyclic Keto Ester LXXIII. One gram of the keto ester (product melting above 139° is suitable) and a solution of 1 g. of sodium in 100 ml. of anhydrous methanol are heated at reflux for two hours under nitrogen. After the solution has been cooled, water is added and the mixture is extracted with two portions of benzene. The benzene solution is washed with water, evaporated, and the residue crystallized from ethyl acetate to yield 0.52 g. of yellow needles, m.p. 174–176°. A second crop (0.23 g., m.p. 160–175°) brings the total to 79%. After the second crystallization from ethyl acetate (Norit), the product LXXIII melts at 178.5–179.5°.

The keto ester can be hydrolyzed and decarboxylated to the tetracyclic ketone LXXIV in 52% yield with aqueous methanolic potassium hydroxide.

Cyclization of the Tricyclic Keto Ester LXXI to Form the Tetracyclic Ketone LXXIV. (a) A mixture of 500 ml. of methanol, 5 ml. of 45% potassium hydroxide, and 0.8 g. of the keto ester LXXI is heated under reflux under a nitrogen atmosphere for twenty hours. The solution is diluted, and the product is extracted with three portions of warm benzene. The extract is washed with water and dilute hydrochloric acid and then concentrated. The first crop of 0.40 g. of yellow plates melts at 182–185°, and the second crop at 176–183°. The total yield is 90%. A sample purified for analysis by evaporative distillation at 0.5 mm. and recrystallized from benzene forms colorless plates, m.p. 188–188.5°.

(b) When 0.5 g. of the diketo ester LXXI is refluxed with 25 ml. of acetic acid and 5 ml. of hydrochloric acid under nitrogen, the product LXXIV obtained by dilution and extraction with benzene weighs 0.32 g. (84%) and melts at 185–187°.

2-Keto-10-methyl-$\Delta^{1,9}$-octalin (LXXV).[25] A mixture of 33 g. of 2-methylcyclohexanone, 6.1 g. of powdered sodium amide, and 50 ml. of dry ether is stirred for four hours in a stream of dry nitrogen at room temperature. A solution of 43 g. of 1-diethylamino-3-butanone methiodide [26] in 20 ml. of absolute ethanol is then slowly added, and after four hours the solution is heated under reflux for two hours. Dilute hydrochloric acid and ether are added, and the ethereal solution is separated, dried, and distilled, giving 9.3 g. (38%) of 2-keto-10-methyl-$\Delta^{1,9}$-octalin, b.p. 143–145°/16 mm.

7-Keto-1-methoxy-13-methyl-5,6,7,9,10,13-hexahydrophenanthrene (LXXVI).[35] Fifteen grams of methyl iodide is added in portions during one-half hour to 15.05 g. of 1-diethylamino-3-butanone [36] (XXIV, R = C_2H_5), which is swirled gently in a 1-l. flask cooled in ice. The swirling is regulated to obtain the crystalline methiodide as an even coating on the walls of the flask. When no more liquid remains, the flask is kept in ice for one-half hour and then under the tap for 45 minutes. A solution of 20.0 g. of 1-methyl-5-methoxy-2-tetralone [35] (LXV) in 100 ml. of dry, thiophene-free benzene is added, the air is expelled from the flask by dry nitrogen, and a solution of potassium ethoxide prepared from 6.5 g. of potassium and 100 ml. of dry ethanol is added with ice cooling during five minutes. Swirling is continued until all the methiodide has dissolved (about 30 minutes) and has been replaced by a precipitate of potassium iodide. After the mixture has been kept in ice for another hour, it is boiled gently for twenty-five minutes. An excess of 2 N sulfuric acid is then added, and the nitrogen stream is stopped. After addition of enough water to dissolve the potassium sulfate, the benzene layer is separated and the aqueous layer extracted twice with ether. The combined organic extracts are washed with water, dried with a little magnesium sulfate, and evaporated. The residue is distilled to yield 23.2 g. of material boiling up to 180°/1 mm. The distillate is warmed until fluid, and ether is added gradually until the total weight is 40 g. Crystallization begins at once and is allowed to proceed at 0° overnight. The product is collected and washed with chilled ether; it weighs 17.0 g. and melts at 115–117°. Fractional distillation of the mother liquors affords an additional gram of material, making the total yield 71%. The process has been carried out successfully on four times the above scale.

Diethyl Skatylacetamidomalonate (XLIV).[41] To a boiling mixture of 1.2 l. of toluene (or xylene) and 17 g. of powdered sodium hydroxide contained in a 5-l. three-necked flask fitted with a mechanical stirrer, a condenser, and a nitrogen inlet tube are added 250 g. (1.43 moles) of gramine [196] (VIIa) and 311 g. (1.43 moles) of diethyl acetamidomalonate (XLI).[45] Refluxing and rapid stirring are continued for five hours while a rapid stream of nitrogen is passed through the reaction mixture. The evolution of dimethylamine, which is very rapid at the beginning, almost ceases at the end of the heating period.

The reaction mixture is filtered through a preheated funnel, and the filtrate is held at 5° for several hours to aid crystallization. The product is collected by filtration and washed with cold toluene followed by petroleum ether. The dried product (446 g., 90%) melts at 158–159°

and can be converted without further purification to $(+, -)$-tryptophan by the method of Snyder and Smith.[45]

Ethyl β-(2-Pyrrolyl)-α-cyano-α-acetamidopropionate (LXXVII).[43] In a flask fitted with a stirrer, a condenser, and a dropping funnel are placed 100 ml. of absolute ethanol and 1.72 g. of clean sodium. After all the sodium has dissolved, 12.7 g. of ethyl acetamidocyanoacetate [203] (XLV) and then 9.3 g. of 2-dimethylaminomethylpyrrole [204] are added. While the flask is cooled in an ice bath and the mixture is stirred, 15.8 g. of dimethyl sulfate is added dropwise at such a rate that the temperature does not exceed 35°. After the addition is complete, the mixture is stirred for one hour and allowed to stand at room temperature for about eight hours. The ethanol is evaporated under reduced pressure, and the residue is diluted with 200 ml. of water and chilled. Nearly white crystals (17 g., 90%) separate. They are purified by dissolving in acetone, treating with charcoal, filtering, diluting with water, and chilling for several hours. The white plates which form melt at 122°.

This material can be hydrolyzed and decarboxylated in one step by treatment with hot sodium hydroxide.

1-Methylskatylmalonic Acid (LXXVIII).[17] To a solution of 0.23 g. (0.01 gram atom) of sodium in 30 ml. of absolute ethanol are added 4.65 g. (0.02 mole) of tricarbethoxymethane [205] and 3.3 g. (0.01 mole) of 1-methylgramine methiodide (IX).[9] The mixture is refluxed for one and one-half hours under a current of nitrogen; there is a vigorous evolution of trimethylamine. While refluxing is continued, 10 ml. of 40% aqueous sodium hydroxide is added, followed, after ten minutes, by 10 ml. of water. Trimethylamine evolution resumes for some time. After about two hours, heating is discontinued and the solution is concentrated under reduced pressure, extracted twice with ether, acidified with concentrated hydrochloric acid, and chilled. The brown crystals which separate are collected and dissolved in 15 ml. of a saturated solution of sodium carbonate and 25 ml. of water. The solution is boiled with Norit, filtered with suction, acidified with concentrated hydrochloric acid and chilled. The light pink crystals after thorough washing with ice water and drying weigh 1.55 g. (62%) and melt at 171–172° (dec.).

A 34.5% yield can be obtained when the alkylation is carried out in aqueous medium.

[203] Tullar, U. S. pat. 2,393,723 [*C. A.*, **40**, 2465 (1946)].

[204] Herz, Dittmer, and Cristol, *J. Am. Chem. Soc.*, **69**, 1698 (1947).

[205] Lund and Voigt, *Org. Syntheses Coll. Vol.* **2**, 594 (1943).

TABULAR SURVEY OF ALKYLATION PRODUCTS

In Tables I–X are summarized carbon-carbon alkylations with amines and ammonium salts reported prior to January 1, 1951. Some more recent references have been included in the text but not in the tables. Certain references may have been overlooked, since there is no sure way of locating the alkylation reactions in the literature.

Yields are given as stated in the original literature. A dash indicates that no yield is reported.

Table I is concerned with carbon-carbon alkylations with aliphatic and aromatic tetraalkylammonium salts other than phenolic Mannich bases which are listed in Table II. Table III contains alkylations with heterocyclic Mannich bases by the Mannich method (p. 113), Table IV similar alkylations by the Robinson method (p. 113), and Table V analogous reactions by the Albertson method (p. 118). Table VI is concerned with alkylations with ketonic Mannich bases; in Table VII are listed alkylations of alkali metal cyanides with the hydrochlorides, and in Table VIII various alkylations with the quaternary salts of such bases. Table IX contains a survey of an alkylation of indole with diethyl piperidinomethylformamidomalonate under a variety of conditions, and in Table X are listed some recently reported alkylations with Mannich bases of nitro compounds.

Within each table, the reactions are arranged in order of complexity of the alkylating group, and, for the same alkylating group, in order of the compounds alkylated, cyanides being listed first, nitro compounds next, then esters and ketones, and last organometallic compounds.

TABLE I
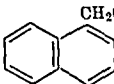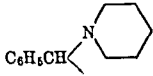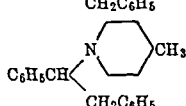
CARBON ALKYLATIONS WITH ALIPHATIC AND AROMATIC TRIALKYLAMINES AND TETRAALKYLAMMONIUM SALTS

Quaternary Salt	Compound Alkylated	Solvent	Product	Yield %	Reference
Tetramethylammonium cyanide		None	Acetonitrile and methylcarbylamine	—	3
Dimethylethylanilinium iodide	Potassium cyanide	None	Acetonitrile	—	4
Tetramethylammonium ethoxide	Diethyl malonate	Ethanol	Diethyl methylmalonate	58	38
Tetramethylammonium chloride	9-Fluoryllithium	None	9-Methylfluorene	—	38
Benzyldimethylanilinium chloride	Potassium cyanide	None	Benzyl cyanide	—	4
Benzyldimethylanilinium chloride	Sodium cyanide	Water	Alkylation failed	—	7
Benzyltrimethylammonium iodide	2-Nitropropane sodium salt	Ethylene glycol	Benzaldehyde	Low	206
Benzyltrimethylammonium bromide	Diethyl sodiomalonate	Di-n-butyl ether	Diethyl benzylmalonate	77	7
Benzyltriethylammonium iodide	Diethyl sodiomalonate	Di-n-butyl ether	Diethyl benzylmalonate	63	7
Benzyldimethylanilinium chloride	Diethyl sodiomalonate	Ethanol	Diethyl benzylmalonate	38	7
Benzyldimethylanilinium chloride	Diethyl sodiomalonate	None	Diethyl benzylmalonate	73–79	7
Benzyldimethylanilinium chloride	Diethyl sodiomalonate	Ethanol (autoclave)	Diethyl benzylmalonate	32–36	7
Benzyldimethylanilinium ethoxide	Diethyl sodiomalonate	Ethanol	Diethyl benzylmalonate	51	7
Benzylmethylpiperidinium chloride	Diethyl sodiomalonate	Ethanol	Diethyl benzylmalonate	5	7
Benzylmethylpiperidinium chloride	Diethyl sodiomalonate	Ethanol (autoclave)	Diethyl benzylmalonate	20–26	7
Benzylmethylpiperidinium iodide	Diethyl sodiomalonate	Ethanol (autoclave)	Diethyl benzylmalonate	22–36	7
Benzylmethylpiperidinium iodide	Diethyl sodiomalonate	Di-n-butyl ether	Diethyl benzylmalonate	43	7
Benzyltrimethylammonium cyanoacetate		None	Hydrocinnamonitrile	—	
			Dibenzylacetonitrile	—	
			Dibenzylmethylamine	—	39
Benzyldimethylamine	Methyl cyanoacetate	None	Hydrocinnamonitrile	15	
			Dibenzylacetonitrile	19	
			Dibenzylmethylamine	23	39
Benzyldimethylanilinium chloride	Ethyl sodioacetoacetate	Ethanol	Ethyl benzylacetoacetate	60	7
Benzyldimethylamine	Tricarbethoxymethane	None	Hydrocinnamic acid	39	
			Dibenzylacetic acid	19	39
Benzyltrimethylammonium bromide	Phenyllithium	Ether	1,1,2-Triphenylethane	—	61
Benzyltrimethylammonium iodide	Phenylmagnesium bromide	Di-n-butyl ether	Biphenyl	25	62

Note: References 206–229 are listed on p. 197.

TABLE I—*Continued*
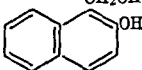
CARBON ALKYLATIONS WITH ALIPHATIC AND AROMATIC TRIALKYLAMINES AND TETRAALKYLAMMONIUM SALTS

Quaternary Salt	Compound Alkylated	Solvent	Product	Yield %	Reference
Benzylpyridinium chloride	Phenylmagnesium bromide	Di-*n*-butyl ether	Biphenyl	4	62
p-Nitrobenzyltrimethylammonium iodide	2-Nitropropane sodium salt	Ethanol	$p\text{-}O_2NC_6H_4CH_2C(CH_3)_2NO_2$	63	206
(+)-α-Phenylethyltrimethylammonium iodide	Sodium cyanide	None	Styrene	—	2
(+)-α-Phenylethyltrimethylammonium iodide	Diethyl sodiomalonate	Diethyl Carbitol	(+, −)-α-Phenylethylmalonic ester	18	2
1-Dimethylaminomethyl-2-methoxynaphthalene methiodide	Sodium cyanide	None	2-Methoxy-1-naphthylacetonitrile	44	6
1-Dimethylaminomethyl-2-methoxynaphthalene methiodide	Diethyl sodiomalonate	Diethyl Carbitol	[naphthalene with $CH_2CH(CO_2H)_2$ and OCH_3 substituents]	61	6
$C_6H_5CH\left(N\bigcirc\right)_2$	Benzylmagnesium chloride	Ether	[piperidine ring with C_6H_5CH and $CH_2C_6H_5$ substituents on N]	19	63
$C_6H_5CH\left(N\bigcirc CH_3\right)_2$	Benzylmagnesium chloride	Benzene	[piperidine ring with CH_3, C_6H_5CH and $CH_2C_6H_5$ substituents]	15	63

Note: References 206–229 are listed on p. 197.
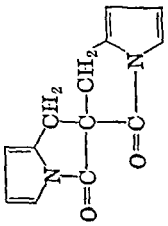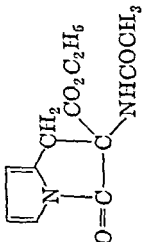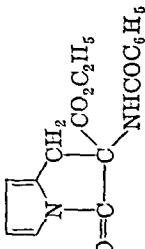
TABLE II

CARBON-CARBON ALKYLATIONS WITH o-HYDROXYBENZYLAMINES

Substituted o-Hydroxybenzylamine	Compound Alkylated	Solvent; Temperature	Product	Yield %	Reference
2-Dimethylaminomethyl-phenol	Phenylmagnesium bromide	Di-n-butyl ether; reflux	—	0	62
2-Dimethylaminomethyl-6-methoxyphenol	Sodium cyanide	90% ethylene glycol, 10% water; reflux	2-Hydroxy-3-methoxy phenylacetic acid	4	15a
2-Dimethylaminomethyl-6-methoxyphenol	Ethyl cyanoacetate	Excess ethyl cyanoacetate; 190°	Resins and N,N-dimethyl-cyanoacetamide	—	15a
2-Dimethylaminomethyl-4-methylphenol	Sodium cyanide	50% ethanol; 150°	2-Hydroxy-5-methylphenyl-acetic acid	—	12
2-Dimethylaminomethyl-4-methyl-6-bromophenol	Sodium cyanide	50% ethanol; 150°	2-Hydroxy-3-bromo-5-methyl-phenylacetic acid	—	12
2-Dimethylaminomethyl-4-allyl-6-methoxyphenol	Sodium cyanide	50% ethanol; 150°	2-Hydroxy-3-methoxy-5-allyl-phenylacetic acid	—	12
2-Diethylaminomethyl-4-allyl-6-methoxyphenol	Sodium cyanide	50% ethanol; 150°	2-Hydroxy-3-methoxy-5-allyl-phenylacetic acid	—	12
1-Dimethylaminomethyl-2-hydroxynaphthalene	Sodium cyanide	50% ethanol; reflux	2-Hydroxy-1-naphthalene-acetic acid	47	12, 15
			Di-2-hydroxy-1-naphthyl-methane	20	15
1-Dimethylaminomethyl-2-hydroxynaphthalene	Hydrogen cyanide	Benzene; 150°	2-Hydroxy-1-naphthalene-acetonitrile	—	12
1-Morpholinomethyl-2-hydroxynaphthalene	Dibenzoyl-methane	Ethanolic HCl; reflux	CH₂CH(COC₆H₅)₂	53	23
1,5-Bis(dimethylaminomethyl)-2,6-dihydroxynaphthalene	Sodium cyanide	50% ethanol; 150°	2,6-Dihydroxynaphthalene-1,5-diacetic acid	—	12
5-Dimethylaminomethyl-6-hydroxyquinoline	Sodium cyanide	50% ethanol; 150°	6-Hydroxyquinoline-5-acetic acid	—	12

For the 1-Morpholinomethyl entry, the product is shown as $CH_2CH(COC_6H_5)_2$ attached to a naphthalene ring system bearing an OH group.

Note: References 206–229 are listed on p. 197.
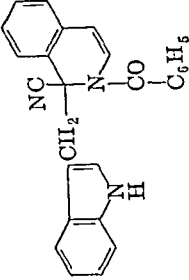
TABLE III

CARBON ALKYLATIONS WITH HETEROCYCLIC COMPOUNDS CONTAINING A DIALKYLAMINOMETHYL GROUP
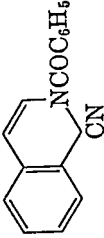
Amine	Compound Alkylated	Solvent; Catalyst	Product	Yield %	Reference
2-Dimethylamino-methylpyrrole	Diethyl malonate	Toluene; NaOH	[pyrrole-CH₂-C(C=O)(C=O)-N structure]	4	43
2-Dimethylamino-methylpyrrole	Diethyl acetamido-malonate	Toluene or xylene; NaOH	[pyrrole-CH₂-C(CO₂C₂H₅)(NHCOCH₃)-C=O structure]	70–80	43
2-Dimethylamino-methylpyrrole	Diethyl benzamido-malonate	Xylene; NaOH	[pyrrole-CH₂-C(CO₂C₂H₅)(NHCOC₆H₅)-C=O structure]	38	43a
Gramine (3-dimethylamino-methylindole)	Sodium cyanide	Ethanol-water; none	Indole-3-acetamide / Indole-3-acetic acid	20 / 69	16
Gramine	Sodium cyanide	Ethanol-water; none	Indole-3-acetic acid	Quant.	12
Gramine	Hydrogen cyanide	Benzene; none	Indole-3-acetonitrile	—	12

3-Diethylamino-methylindole	Sodium cyanide	Ethanol-water; none	Indole-3-acetic acid	—	12
3-Piperidino-methylindole	Hydrogen cyanide	Benzene; none	Indole-3-acetonitrile	—	12
Gramine	Nitromethane	Excess nitro-methane; NaOH	Diskatylnitromethane *	20	18
Gramine	Nitroethane	Excess nitroeth-ane; NaOH	1-Nitro-1-skatylethane *	20	18
Gramine	1-Nitropropane	Excess 1-nitropro-pane; NaOH	1-Nitro-1-skatylpropane *	82-95	18
Gramine	2-Nitropropane	Excess 2-nitropro-pane; NaOH	2-Nitro-2-skatylpropane *	85	18
Gramine	2-Nitro-1-butanol	Excess 2-nitro-1-butanol	Alkylation failed		18
Gramine	Ethyl nitroacetate	Ethanol; NaOH	Ethyl diskatylnitroacetate *	80	18
Gramine	Ethyl nitroacetate	Xylene; none	Ethyl skatylnitroacetate *	90	19
Gramine	Diethyl nitromalonate	Toluene; none	Diethyl skatylnitromalonate *	97	20
Gramine	Diethyl malonate	Excess diethyl malonate; Na	Diethyl skatylmalonate *	76	7
Gramine	Tricarbethoxymethane	Excess tricar-bethoxymeth-ane; none	Skatylmalonic acid *	67	17
3-Diethylamino-methylindole	Diethyl formamido-malonate	Toluene; NaOH	Diethyl skatylformamidomalonate *	98	52a
Gramine	Diethyl acetamido-malonate	Xylene or tolu-ene; NaOH	Diethyl skatylacetamidomalonate *	90	41
Gramine	Diethyl acetamido-malonate	Pyridine; none	Diethyl skatylacetamidomalonate *	48	41

TABLE III—Continued

CARBON ALKYLATIONS WITH HETEROCYCLIC COMPOUNDS CONTAINING A DIALKYLAMINOMETHYL GROUP

Amine	Compound Alkylated	Solvent; Catalyst	Product	Yield %	Reference
Gramine	Diethyl acetamidomalonate	Pyridine; NaOH	Diethyl skatylacetamidomalonate *	55	41
Gramine	Diethyl acetamidomalonate	No solvent; none	Diethyl skatylacetamidomalonate *	54	41
3-Diethylaminomethylindole	Diethyl acetamidomalonate	Toluene; NaOH	Diethyl skatylacetamidomalonate *	86	41
3-Piperidinomethylindole	Diethyl acetamidomalonate	Toluene; NaOH	Diethyl skatylacetamidomalonate *	64	41
Gramine	Diethyl phthalimidomalonate	Toluene; NaOH	Diethyl skatylphthalimidomalonate *	10	41
Gramine	Phenylmagnesium bromide	Di-n-butyl ether; none	3-Benzylindole	3	62
Gramine	(1,2-dihydroisoquinoline; CN, NCOC₆H₅ structure)	Xylene; Na	(isoquinoline structure: NC, CH₂–(1H-indol-3-yl), N–CO–C₆H₅)	46	102a
1-Methylgramine	Sodium cyanide	Ethanol-water; none	Alkylation failed		17
1-Methylgramine	Methyl cyanoacetate	Excess methyl cyanoacetate; none	Di-(1-methyl-3-indolyl)methane	10	
			1-Methylskatylmalonic acid *	18	17, 39

Amine	Reagent	Conditions	Product	Yield (%)	Refs.
1-Methylgramine	Ethyl cyanoacetate	Excess ethyl cyanoacetate; Na	Di-(1-methyl-3-indolyl)methane	11	
			1-Methylskatylmalonic acid *	15	17
1-Methylgramine	Tricarbethoxymethane	Excess tricarbethoxymethane; none	1-Methylskatylmalonic acid *	15	17
			3'-(1-Methyl-3-indolyl)propionic acid	9	
1-Methylgramine	Diethyl acetamido-malonate	Excess diethyl acetamidomalonate; Na	1-Methylskatylacetamidomalonic acid *	4	17
			1-Methyl-N-acetyltryptophan	8	62
			Di-(1-methyl-3-indolyl)methane	15	
1-Methylgramine	Methylmagnesium iodide	Di-n-butyl ether; none	Alkylation failed	18 †	207
4-Chlorogramine	Potassium cyanide	Ethanol-water; none	4-Chloroindole-3-acetamide	—	53
5-Bromogramine	Diethyl acetamido-malonate	Xylene; NaOH	Diethyl 5-bromoskatylacetamido-malonate*	76	54
6-Methylgramine	Ethyl acetamidocyano-acetate	Xylene; NaOH	Ethyl 6-methylskatylacetamidocyano-acetate *	61	55
3-Diethylamino-methyl-2-carbethoxyindole	Diethyl acetamidomalonate	Xylene; NaOH	Diethyl 2-carbethoxyskatylacetamido-malonate *	69	
3 Dimethylamino-methyl-2-carbethoxyindole		Xylene; Na			102a

Reagent structure (isoquinoline derivative): NCOC$_6$H$_5$, CN

Product structure: NC, CH$_2$, CO$_2$C$_2$H$_5$, N–CO–C$_6$H$_5$ (with indole N–H)

Note: References 206–229 are listed on p. 197.

TABLE III—*Continued*

CARBON ALKYLATIONS WITH HETEROCYCLIC COMPOUNDS CONTAINING A DIALKYLAMINOMETHYL GROUP

Amine	Compound Alkylated	Solvent; Catalyst	Product	Yield %	Reference
3-Dimethylaminomethylindole-2-carboxypiperidide	Diethyl acetamidomalonate	Xylene; NaOH		50 ‡	208
2-Phenyl-3-dimethylaminomethylindole	Sodium cyanide	Ethanol-water; none	2-Phenylindole-3-acetic acid	—	12
3-Piperidinomethylindazole	Diethyl nitromalonate	Xylene; NaOH	Alkylation failed		209
3-Piperidinomethylindazole	Diethyl acetamidomalonate	Toluene; none	Alkylation failed		209

Note: References 206–229 are listed on p. 197.

* The skatyl group is

† The yield was based on the acid obtained by hydrolysis of the amide.
‡ Over-all yield from indole-2-carboxypiperidide.

TABLE IV

CARBON ALKYLATIONS WITH SALTS OF HETEROCYCLIC COMPOUNDS CONTAINING A TRIALKYLAMINOMETHYL GROUP
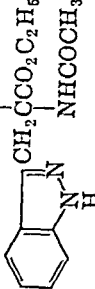
Quaternary Salt	Compound Alkylated	Solvent	Product	Yield %	Reference
Furyltrimethylammonium iodide	Sodium cyanide	Water or none	2-Furylacetonitrile	22–32	10
2-Dimethylaminomethyl-5-methylfuran methiodide	Sodium cyanide	Water	5-Methyl-2-furonitrile	4–5	10
			5-Methyl-2-furylacetonitrile	37	10
2-Dimethylaminomethyl-pyrrole methiodide	Diethyl sodioacetamido-malonate	Dioxane		53	43
2-Dimethylaminomethyl-pyrrole methiodide	Methylmagnesium iodide	Di-n-butyl ether	Alkylation failed		62
Gramine (3-dimethylamino-methylindole) methiodide	Potassium silver cyanide	Water	Indoleacetonitrile	46	7
Gramine methiodide	Diethyl sodiomalonate	Di-n-butyl ether	Skatylmalonic acid *	85	7
Gramine ethiodide	Diethyl sodiomalonate	Not reported	Diethyl skatylmalonate *	—	47
Gramine methiodide	Ethyl sodiocyanoacetate	Di-n-butyl ether	Diethyl skatylcyanoacetate *	85	7
Gramine methiodide	Ethyl sodioacetoacetate	Di-n-butyl ether	Ethyl skatylacetoacetate *	—	7
Gramine ethiodide	Ethyl sodioacetoacetate	Ethanol	Ethyl skatylacetoacetate *	—	50
Gramine methiodide	Diethyl sodioacetamido-malonate	Dioxane	Diethyl skatylacetamido-malonate *	63–70	45, 46
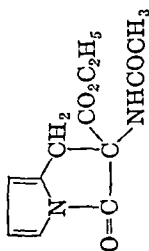
Note: References 206–229 are listed on p. 197.

TABLE IV—Continued

CARBON ALKYLATIONS WITH SALTS OF HETEROCYCLIC COMPOUNDS CONTAINING A TRIALKYLAMINOMETHYL GROUP

Quaternary Salt	Compound Alkylated	Solvent	Product	Yield %	Reference
Gramine methiodide	Diethyl sodioacetamidomalonate	Ethanol	Diethyl skatylacetamidomalonate *	—	46
Gramine ethiodide	Diethyl sodioacetamidomalonate	—	Diethyl skatylacetamidomalonate *	—	47
Gramine ethiodide	Diethyl sodiobenzamidomalonate	—	Diethyl skatylbenzamidomalonate *	—	47
Gramine ethiodide	Diethyl sodiophthalimidomalonate	Di-n-butyl ether	Diethyl skatylphthalimidomalonate *	—	46
Gramine methiodide	Methylmagnesium iodide	Di-n-butyl ether	3-Ethylindole	8	62
			sym-Di-3-indolylethane	16	62
Gramine methiodide	Phenylmagnesium bromide	Di-n-butyl ether	3-Benzylindole	24	62
			sym-Di-3-indolylethane	17	62
Gramine methiodide	Benzylmagnesium chloride	Di-n-butyl ether	3-(Phenethyl)indole	14	62
1-Methylgramine methiodide	Sodium cyanide	Water	1-Methylindole-3-acetonitrile	60–64	9
			1,3-Dimethyl-2-cyanoindole	4	17
1-Methylgramine methiodide	Diethyl sodiomalonate	Ethanol or excess diethyl malonate	1-Methylskatylmalonic acid *†	22	17
1-Methylgramine methiodide	Ethyl sodiocyanoacetate	Excess ethyl cyanoacetate	1-Methylskatylmalonic acid *†	17	17
1-Methylgramine methiodide	Tricarbethoxymethane sodium enolate	Ethanol	1-Methylskatylmalonic acid *†	63	17
1-Methylgramine methiodide	Tricarbethoxymethane sodium enolate	Water	1-Methylskatylmalonic acid *†	35	17

1-Methylgramine methiodide	Diethyl sodiocyanomalonate	Water or ethanol	1-Methylskatylmalonic acid *,†	51	17
1-Methylgramine methiodide	Ethyl sodioacetamidocyanoacetate	Ethanol	Ethyl 1-methylskatylacetamidocyanoacetate *	69	48
1-Methylgramine methiodide	1-Methylindole	Aqueous ethanol	Di-(1-methyl-3-indolyl)-methane	49	17
1-Methylgramine methiodide	Methylmagnesium iodide	Di-n-butyl ether	1-Methyl-3-ethyl indole	44	62
1-Methylgramine methiodide	Phenylmagnesium bromide	Di-n-butyl ether	1-Methyl-3-benzyl indole	73	62
1-Methyl-5-methoxygramine methiodide	Diethyl sodioacetamidomalonate	Ethanol	Diethyl 1-methyl-5-methoxyskatylacetamidomalonate *	86	210
3-Piperidinomethylindazole methiodide	Diethyl sodioacetamidomalonate	Ethanol	[indazole] $CH_2C(CO_2C_2H_5)_2$ $NHCOCH_3$	35 †	209
3-Dimethylaminomethylindazole methiodide	Ethyl sodioacetamidocyanoacetate	Ethanol	[indazole] CN $CH_2CCO_2C_2H_5$ $NHCOCH_3$	—	209

Note: References 206–229 are listed on p. 197.

* The skatyl group is [structure]
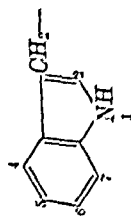
† The acid was obtained by hydrolysis of the primary alkylation product.

TABLE V

CARBON ALKYLATIONS WITH HETEROCYCLIC COMPOUNDS CONTAINING A DIALKYLAMINOMETHYL GROUP USING DIMETHYL SULFATE OR ETHYL IODIDE AS A QUATERNIZING AGENT

Amine	Compound Alkylated	Solvent; Quaternizing Agent	Product	Yield %	Reference
2-Dimethylaminomethyl-pyrrole	Diethyl sodiomalonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2CH(CO_2C_2H_5)_2$*	33, 44	43, 43a
			$(2\text{-}C_4H_4NCH_2)_2C(CO_2C_2H_5)_2$*	Low	43a
2-Dimethylaminomethyl-pyrrole	Diethyl sodiomalonate (2 moles)	Ethanol; dimethyl sulfate	$(2\text{-}C_4H_4NCH_2)_2C(CO_2C_2H_5)_2$	38	43a
2-Dimethylaminomethyl-pyrrole	Ethyl sodiocyanoacetate	Ethanol; dimethyl sulfate	$(2\text{-}C_4H_4NCH_2)_2C(CN)CO_2C_2H_5$*	30	43
2-Dimethylaminomethyl-pyrrole	Tricarbethoxymethane sodium enolate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2CH(CO_2C_2H_5)_2$*	26	43a
			$(2\text{-}C_4H_4NCH_2)_2C(CO_2C_2H_5)_2$*	—	43a
2-Dimethylaminomethyl-pyrrole	Diethyl sodiomethyl-malonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\underset{CH_3}{C}(CO_2C_2H_5)_2$*	55	43a
2-Dimethylaminomethyl-pyrrole	Diethyl sodiophenyl-malonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\underset{C_6H_5}{C}(CO_2C_2H_5)_2$*	63	43a
2-Dimethylaminomethyl-pyrrole	Diethyl sodioacetoxy-malonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\underset{OCOCH_3}{C}(CO_2C_2H_5)_2$*	27	43a
2-Dimethylaminomethyl-pyrrole	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\underset{NHCOCH_3}{C}(CO_2C_2H_5)_2$*	94	43
2-Dimethylaminomethyl-pyrrole	Diethyl sodiobenzamido-malonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\underset{NHCOC_6H_5}{C}(CO_2C_2H_5)_2$*	84	43a
2-Dimethylaminomethyl-pyrrole	Ethyl sodioacetamido-cyanoacetate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2\overset{CN}{\underset{NHCOCH_3}{C}}CO_2C_2H_5$*	90	43

Amine	Reagent	Conditions	Product	Yield (%)	Reference
2-Dimethylaminomethyl-pyrrole	Diethyl sodiophthalimidomalonate	Ethanol; dimethyl sulfate	$2\text{-}C_4H_4NCH_2C(CO_2C_2H_5)_2$* (phthalimido, N bearing two CO groups)	Low	43
2,5-Bis(piperidinomethyl)-pyrrole	Diethyl sodioacetamidomalonate	Ethanol; dimethyl sulfate	$(H_5C_2O_2C)_2CCH_2$ / CH_3CONH — pyrrole ring — $CH_2C(CO_2C_2H_5)_2$ / $NHCOCH_3$	100	44
2-Acetamido-5-dimethyl-aminomethylthiazole hydrochloride	Diethyl sodioacetamidomalonate	Ethanol; diethyl sulfate and sodium ethoxide	$CH=CCH_2C(CO_2C_2H_5)_2$ / $NHCOCH_3$ (thiazole, $NHCOCH_3$)	—	44
2-Acetamido-4-methyl-5-dimethylaminomethyl-thiazole hydrochloride	Diethyl sodiomalonate	Ethanol; dimethyl sulfate	$H_3CC=CCH_2CH(CO_2C_2H_5)_2$ (thiazole, $NHCOCH_3$)	48.5	44
2-Acetamido-4-methyl-5-dimethylaminomethyl-thiazole	Diethyl sodioacetamidomalonate	Ethanol; dimethyl sulfate	$H_3CC=CCH_2C(CO_2C_2H_5)_2$ / $NHCOCH_3$ (thiazole, $NHCOCH_3$)	50	44
Gramine (3-dimethylam-inomethylindole)	Potassium cyanide	Aqueous ethanol; dimethyl sulfate	Indole-3-acetonitrile	50 †	8
Gramine	Diethyl sodioacetamido-malonate	Ethanol; ethyl iodide	Diethyl skatylacetamidomalonate ‡	65, 82, 86	40, 50
Gramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate (1 mole)	Diethyl skatylacetamidomalonate ‡	72, 82	40, 8

TABLE V—Continued

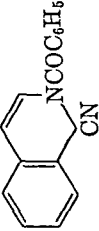CATION ALKYLATIONS WITH HETEROCYCLIC COMPOUNDS CONTAINING A DIALKYLAMINOMETHYL GROUP USING DIMETHYL SULFATE OR ETHYL IODIDE AS A QUATERNIZING AGENT
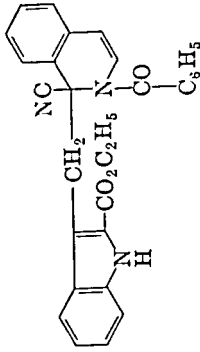
Amine	Compound Alkylated	Solvent; Quaternizing Agent	Product	Yield %	Reference
Gramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate (1.65 mole)	Diethyl skatylacetamidomalonate ‡	95	40
Gramine	Diethyl sodiobenzamido-malonate	Ethanol; dimethyl sulfate	Diethyl skatylbenzamidomalonate ‡	50	40
Gramine	Ethyl sodioacetamido-cyanoacetate	Ethanol; dimethyl sulfate	Ethyl skatylacetamidocyanoacetate ‡	98	49
3-Piperidinomethylindole	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl skatylacetamidomalonate ‡	—	40
3-Diethylaminomethyl-indole	Ethyl sodioacetamido-acetoacetate	Ethanol; dimethyl sulfate	Ethyl skatylacetamidoacetoacetate ‡	83	22
Gramine	Diethyl sodiobenzamido-malonate	Ethanol; ethyl iodide	Diethyl skatylbenzamidomalonate ‡	—	50
Gramine	Diethyl sodiophthalim-idomalonate	Ethanol; ethyl iodide	Diethyl skatylphthalimidomalonate ‡	—	50
Gramine	Ethyl sodiosuccinimido-cyanoacetate	Ethanol; ethyl iodide	Ethyl skatylsuccinimidocyanoacetate ‡	—	50
Gramine	Ethyl sodiophthalimido-acetoacetate	Ethanol; ethyl iodide	Ethyl skatylphthalimidoacetoacetate ‡	—	50
Gramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 5-methoxyskatylacetamido-malonate ‡	91	210
5-Methoxygramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 2-methylskatylacetamido-malonate ‡	80	51
2-Methylgramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 4-methylskatylacetamido-malonate ‡	82	51
4-Methylgramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 5-methylskatylacetamido-malonate ‡	85	51
5-Methylgramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 6-methylskatylacetamido-malonate ‡	79	51
6-Methylgramine	Diethyl sodioacetamido-malonate	Ethanol; dimethyl sulfate	Diethyl 7-methylskatylacetamido-malonate ‡	93	51
7-Methylgramine	Diethyl sodioacetamido-malonate				

Amine	Reagent	Solvent	Product	Yield %	Ref.
4-Cyanogramine	Diethyl sodiomalonate	Ethanol; dimethyl sulfate	Diethyl 4-cyanoskatylmalonate ‡	65	42
3-Diethylaminomethyl-5-methylindole	Ethyl sodioacetamidocyanoacetate	Ethanol; dimethyl sulfate	Ethyl 5-methylskatylacetamidocyano-acetate ‡	87	52
2-β-Dimethylaminoethyl-quinoline	Diethyl sodiomalonate	Ethanol; dimethyl sulfate	quinoline-$CH_2CH_2CHCO_2C_2H_5$, R; R = $CO_2C_2H_5$	43	39a
2-β-Dimethylaminoethyl-quinoline	Ethyl sodioacetoacetate	Ethanol; dimethyl sulfate	quinoline-$CH_2CH_2CHCO_2C_2H_5$, R; R = $COCH_3$	44	39a
2-β-Dimethylaminoethyl-quinoline	Ethyl sodiobenzoyl-acetate	Ethanol; dimethyl sulfate	quinoline-$CH_2CH_2CHCO_2C_2H_5$, R; R = COC_6H_5	33	39a
2-β-Dimethylaminoethyl-quinoline	Diethyl sodiomalonate	Ethanol; dimethyl sulfate	quinoline-CH_2=$CCH_2N(CH_3)_2$(?)	21	39a
			quinoline-CH_2=$CCH_2CH(CO_2C_2H_5)_2$(?)	28	39a

Note: References 206–229 are listed on p. 197.

* 2-C_4H_4N represents

† The yield was based on the acid obtained by hydrolysis of the nitrile.
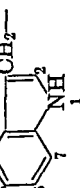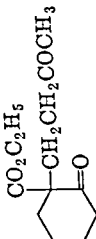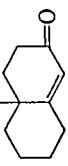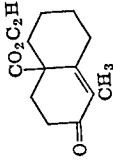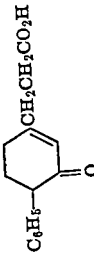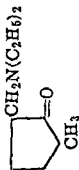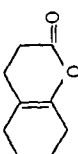
‡ The skatyl group is
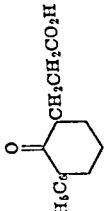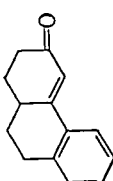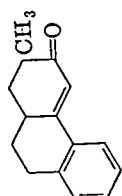
TABLE VI

ALKYLATIONS OF ACTIVE METHYLENE COMPOUNDS WITH β-AMINOKETONES

β-Aminoketone	Active Methylene Compound (Condensing Agent)	Yield %	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1-Dimethylamino-3-butanone	Nitromethane (NaOCH₃)	—	1-Nitro-4-butanone	—	—	—	—	21
1-Dimethylamino-3-butanone	Diethyl malonate (NaOC₂H₅)	—	$CH_3COCH_2CH_2CH(CO_2C_2H_5)_2$	43	NaOC₂H₅	1,3-Cyclohexanedione	—	56
1-Dimethylamino-3-butanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	—	3-Methyl-4-carbethoxy-2-cyclohexen-1-one	18	56
1-Dimethylamino-3-butanone		—	—	—	—	3-Methyl-2-cyclohexen-1-one	—	56
1-Dimethylamino-3-butanone	Ethyl isopropyl-acetoacetate (NaOC₂H₅)	—	—	—	—	4-Carbethoxy-4-isopropyl-3-methyl-2-cyclohexen-1-one (with $CO_2C_2H_5$)	—	211
1-Diethylamino-3-butanone	2-Carbethoxycyclohexanone (NaOC₂H₅)	—	(cyclohexanone with $CH_2CH_2COCH_3$ and $CO_2C_2H_5$)	53	Mg + I₂	2-Keto-10-phenyl-$\Delta^{1,9}$-octalin	42	30
1-Dimethylamino-3-butanone	2-Phenylcyclohexanone (NaNH₂)	—	—	—	—	(bicyclic structure with $CO_2C_2H_5$, CH_3, $=O$)	40	211
1-Diethylamino-3-pentanone	2-Carbethoxycyclohexanone (NaOC₂H₅)	—	—	—	—	—	—	212
4-Keto-6-dimethylamino-caproic acid hydrochloride	Diethyl malonate (NaOC₂H₅)	—	$HO_2C(CH_2)_2CO(CH_2)_2CH(CO_2C_2H_5)_2$	78	—	—	—	—
4-Keto-6-dimethylamino-caproic acid hydrochloride	Phenylacetone (KOC₄H₉-t)	—	—	—	—	(cyclohexenone with C_6H_5, $CH_2CH_2CO_2H$, $=O$)	40	212

Reactant	Reagent (Catalyst)	Product		Conditions	Product		Ref.
β-Dimethylaminopropiophenone	Nitromethane (KOH + CH₃OH)	γ-Nitrobutyrophenone	23	Zn(Hg) + HCl	2-Phenylpyrrolidine	53	21
β-Dimethylaminopropiophenone	Nitromethane (KOH + CH₃OH)	$(C_6H_5COCH_2CH_2)_2CHNO_2$	—	—	—	—	21
β-Dimethylaminopropiophenone	Nitromethane (KOH + CH₃OH)	$(C_6H_5COCH_2CH_2)_3CNO_2$	—	—	—	—	21
β-Dimethylaminopropiophenone hydrochloride	Cyclohexanone (NaOH + H₂O + C₂H₅OH)	[bicyclic ketone structure]	52	HCl + CH₃CO₂H	[structure, C_6H_5, $O=C$]	91	213
β-Dimethylaminopropiophenone	Ethyl acetoacetate (NaOC₂H₅)	$C_6H_5COCH_2CH_2CH(CO_2C_2H_5)COCH_3$	8	—	3-Phenyl-6-carbethoxy-2-cyclohexen-1-one; 3-Phenyl-2-cyclohexen-1-one	—	214
β-Dimethylamino-4-methoxypropiophenone	Nitromethane (NaOCH₃)	γ-Nitro-4-methoxybutyrophenone	—	—	—	—	21
β-Dimethylamino-3,4-dimethoxypropiophenone	Nitromethane (NaOCH₃)	γ-Nitro-3,4-dimethoxybutyrophenone; [structure $(CH_3O\!-\!C_6H_3\!-\!COCH_2CH_2)_2CHNO_2$]	— —	— —	— —	— —	21
[cyclopentanone structure, $CH_2N(C_2H_5)_2$, O, CH_3]	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	[hydrindanone structure, $CO_2C_2H_5$, O, CH_3]	18	25
2-Dimethylaminomethylcyclohexanone	Nitromethane (NaOCH₃)	2-β-Nitroethylcyclohexan-1-one	72	—	—	—	21
2-Dimethylaminomethylcyclohexanone	Diethyl malonate (NaOC₂H₅)	[cyclohexanone structure, $CH_2CH(CO_2C_2H_5)_2$, O]	87	KOH + C₂H₅OH; then (CH₃CO)₂O	[bicyclic lactone structure, O]	—	57
2-Dimethylaminomethylcyclohexanone	Diethyl malonate (None)	[cyclohexanone structure, $CH_2CH(CO_2C_2H_5)_2$, O]	61	—	—	—	215
2-Dimethylaminomethylcyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	2-Keto-3-carbethoxy-9-hydroxydecalin	73	24

Note: References 206–229 are listed on p. 197.

TABLE VI—*Continued*

ALKYLATIONS OF ACTIVE METHYLENE COMPOUNDS WITH β-AMINOKETONES

β-Aminoketone	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield % Alkylation	Cyclizing Agent	Cyclized Product	Yield %	Reference
2-Dimethylaminomethyl-6-methylcyclohexanone	Diethyl malonate (None)	—	Alkylation failed	—	—	—	215
	Diethyl malonate (NaOH suspended in xylene)	$CH_2CH_2CO_2H$	50	—	—	—	58a
2-Dimethylaminomethyl-6-phenylcyclohexanone	Diethyl malonate (NaOH suspended in xylene)	—	—	—		36	24
$CH_2N(CH_3)_2$	Ethyl acetoacetate (NaOC$_2$H$_5$)	—	—	—			
$CH_2N(CH_3)_2$	Ethyl methylacetoacetate (NaOC$_2$H$_5$)	—	—	—	CH_3	21	24

Note: References 206–229 are listed on p. 197.
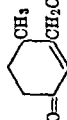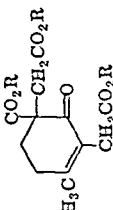
TABLE VII

ALKYLATIONS OF ALKALI CYANIDES WITH β-AMINOKETONE HYDROCHLORIDES

β-Aminoketone (as hydrochloride)	Product	Yield %	Reference
β-Dimethylaminopropiophenone	β-Benzoylpropionitrile	67	13
β-Dimethylamino-4-chloropropiophenone	β-(4-Chlorobenzoyl)propionitrile	32	13
β-Dimethylamino-4-bromopropiophenone	β-(4-Bromobenzoyl)propionitrile	63	13
β-Dimethylamino-3-nitropropiophenone	Resins	—	13
β-Dimethylamino-3-hydroxypropiophenone	β-(3-Hydroxybenzoyl)propionitrile	—	13
β-Dimethylamino-4-hydroxypropiophenone	β-(4-Hydroxybenzoyl)propionitrile	59	13
β-Dimethylamino-3-methoxypropiophenone	β-(3-Methoxybenzoyl)propionitrile	73	13
β-Dimethylamino-4-methoxypropiophenone	β-(4-Methoxybenzoyl)propionitrile	71	13
β-Dimethylamino-3,4-dimethoxypropiophenone	β-(3,4-Dimethoxybenzoyl)propionitrile	85	13
β-Dimethylamino-3,4,5-trimethoxypropiophenone	β-(3,4,5-Trimethoxybenzoyl)propionitrile	65	216
β-Dimethylamino-4-methylpropiophenone	β-(4-Methylbenzoyl)propionitrile	52	13
α-Dimethylaminomethylpropiophenone	Resin or oil	—	13
β-Dimethylaminopivalophenone	Isobutyrophenone	68	11
β-Dimethylaminoethyl α-naphthyl ketone	β-(1-Naphthoyl)propionitrile	43	13
β-Dimethylaminoethyl β-naphthyl ketone	β-(2-Naphthoyl)propionitrile	38	13
2-Dimethylaminomethylcyclohexanone	Resin or oil	—	13
β-Dimethylaminoethyl 2-furyl ketone	β-(2-Furoyl)propionitrile	57	13
β-Dimethylaminoethyl 2-thienyl ketone	β-(2-Thenoyl)propionitrile	67	13
β-Dimethylaminoethyl 2-benzofuranyl ketone	β-(2-Coumarilyl)propionitrile	21	13

Note: References 206–229 are listed on p. 197.

TABLE VIII

Carbon Alkylations with Methiodides of β-Aminoketones

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1-Morpholino-3-butanone	Diethyl malonate (NaOC$_2$H$_5$)	CH$_3$COCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$	17	—	—	—	58
1-Diethylamino-3-butanone	Ethyl acetoacetate (KOC$_2$H$_5$)	CH$_3$COCH(CO$_2$C$_2$H$_5$)CH$_2$CH$_2$COCH$_3$	57	NaOC$_2$H$_5$	3-Methyl-4-carbethoxy-2-cyclohexen-1-one	—	37
1-Morpholino-3-butanone	Ethyl isopropylacetoacetate (NaOC$_2$H$_5$)	—	—	KOH	3-Methyl-6-isopropyl-2-cyclohexen-1-one (piperitone)	50	32,32a
1-Diethylamino-3-butanone	OC⟨CH(CH$_3$)CO$_2$CH$_3$ / CH$_2$CH$_2$CO$_2$CH$_3$ (NaOCH$_3$)	—	—	—		10	217
1-Diethylamino-3-butanone	CO⟨CH(CO$_2$R)CH$_2$CO$_2$R / CH$_2$CH$_2$CO$_2$R (NaOCH$_3$) (R = CH$_3$, C$_2$H$_5$)	—	—	—		44	217a
2-Methylcyclopentanone (NaNH$_2$)		•	—	NaOC$_2$H$_5$		29	25, 218
2-Methylcyclohexanone (NaNH$_2$)		—	—	—	10-Methyl-2-keto-Δ^{1,9}-octalin	38	25
1-Diethylamino-3-pentanone	1,3-Cyclohexanedione (?)	—	—	? †	1-Methyl-2,5-diketo-Δ^{1,9}-octalin	—	219

Amine	Product (base)	Structure	%	Conditions	%	Structure	%	Ref.
1-Diethylamino-3-butanone	2-Methyl-1,3-cyclohexanedione (NaOCH₃)	—	—	—	—	(methyl cyclohexenone; CH₃, O, H₃C)	50	220
1-Diethylamino-3-butanone	2-Carbethoxycyclohexanone (NaOC₂H₅)	—	—	—	—	CH₂CH₂CO₂H, 10-Carbethoxy-2-keto-Δ¹,⁹-octalin	38	25
1-Diethylamino-3-butanone	2-Carbomethoxycycloheptanone (NaOCH₃)	(CH₂)₄, CH₂ COCH₃, CO, C, CH₂ CH₂, CO₂CH₃	86	KOH + H₂O + CH₃OH	—	(CH₂)₅ CH CO CH₂, C CH CH₂	65	27
1-Diethylamino-3-butanone	2-Carbomethoxycyclooctanone (NaOCH₃)	(CH₂)₅, CH₂ COCH₃, CO, C, CH₂ CH₂, CO₂CH₃	78	HCl + CH₃CO₂H	78	(CH₂)₆ CH CO CH₂, C CH CH₂	14	28
1-Diethylamino-3-butanone	2-Carbomethoxycyclononanone (NaOCH₃)	(CH₂)₆, CH₂ COCH₃, CO, C, CH₂ CH₂, CO₂CH₃	79	HCl + CH₃CO₂H	79	(CH₂)₅ C—CH₃ CH—CH₂ CO, (CH₂)₆ C—CH₃ CH—CH₂ CO	32	28
1-Diethylamino-3-butanone	2-Carbomethoxycyclodecanone (NaOCH₃)	(CH₂)₇, CH₂ COCH₃, CO, C, CH₂ CH₂, CO₂CH₃	78	HCl + CH₃CO₂H	78	(CH₂)₇ C—CH₃ CH—CH₂ CO	76	28
1-Diethylamino-3-butanone	2-Carbomethoxycyclotridecanone (NaOCH₃)	(CH₂)₁₀, CH₂ COCH₃, CO, C, CH₂ CH₂, CO₂CH₃	—	HCl + CH₃CO₂H	—	(CH₂)₁₀ C═C—CH₃ CH—CH₂ CO	70	28
							—	29

Note: References 206–229 are listed on p. 197.

TABLE VIII—Continued

Carbon Alkylations with Methiodides of β-Aminoketones

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1-Diethylamino-3-butanone	2-Carbomethoxycyclopentadecanone (NaOCH₃)	[structure: (CH₂)₁₂ ring with CO, C(CO₂CH₃), CH₂CH₂COCH₃]	78	HCl + CH₃CO₂H	[structure: (CH₂)₁₂ ring, CO, C=C–CH₃, CH₂, CH–CH₂]	90	27
				KOH + H₂O + CH₃OH	[structure: (CH₂)₁₂ ring, CO, C–C–CH₃, CH–CH₂]	81	27
				NaOCH₃	6-Cyclohexyl-10-carbomethoxy-2-keto-$\Delta^{1,9}$-octalin	17	221
1-Dimethylamino-3-butanone	[structure: cyclohexanone ring with CO₂CH₃, C₆H₁₁, CH₂CH₂–CO–CH₃] (NaOCH₃)	[structure: cyclohexanone with CO₂CH₃, CH₃, C₆H₁₁, CH₂—CH₂—CO—CH₃]	94	KOH + H₂O + HCl + CH₃CO₂H	6-Cyclohexyl-2-keto-$\Delta^{1,9}$-octalin	48‡	221
					6-Cyclohexyl-2-keto-$\Delta^{1,9}$-octalin	Quant. (crude)	221
				KOH + CH₃OH	6-Cyclohexyl-2-keto-$\Delta^{1,9}$-octalin	12–20‡	221
1-Dimethylamino-3-butanone	[structure: cyclohexanone ring with COCO₂CH₃, C₆H₁₁] (NaOCH₃)	Not isolated	—				
				HCl + CH₃CO₂H	6-Cyclohexyl-2-keto-$\Delta^{1,9}$-octalin	76	47 (72‡)	221
1-Dimethylamino-3-butanone	[structure: cyclohexanone ring with HOCH=, C₆H₁₁] (NaOCH₃)	[structure: cyclohexanone with CHO, C₆H₁₁, CH₂—CH₂—CO—CH₃]	21	KOH + H₂O	6-Cyclohexyl-2-keto-$\Delta^{1,9}$-octalin	68 (82‡)	221

1-Diethylamino-
3-butanone

(NaOH)

CHO, CH₂CH₂COCH₃

CH₂CH₂COCH₃

81-88

83-90
73 over-all

30x

30x

1-Diethylamino-
3-butanone

CHO, CH₂CH₂COCH₃

CH₂CH₂COCH₃

Viscous oil

91-100

30x

30x

1-Diethylamino-
3-butanone

(stereoisomer of above)
(NaOH)

---

trans-β-Decalone
(NaNH₂)

25 · 29

2-Keto-Δ⁹,¹⁰-octalin
(KOC₂H₅)

222 · 13

1-Diethylamino-
3-butanone

(NaNH₂)

223 · 8

Note: References 206–229 are listed on p. 197.

TABLE VIII—*Continued*

CARBON ALKYLATIONS WITH METHIODIDES OF β-AMINOKETONES

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1-Diethylamino-3-butanone	(CH₃ steroid, NaNH₂)	—	—	—	(CH₃ cyclized)	12	218
1-Diethylamino-3-butanone	1-Hydroxymethylene-2-keto-$\Delta^{9,10}$-octalin (KOC₂H₆)	(OH, (?))	—	KOH	(cyclized)	11	222
1-Diethylamino-3-butanone	(OCH₃, NaNH₂)	—	—	—	(OCH₃ cyclized)	28	224
1-Diethylamino-3-butanone	(CO₂C₂H₅, NaNH₂)	—	—	—	(CO₂C₂H₅ cyclized)	16	22A
1-Diethylamino-3-butanone	(CH₃, NaNH₂)	—	—	—	(cyclized)	—	34

30a	80-88 (72 overall)		
30a	85		
30a	50		
30a / 31	6 / 19		
225	55		
33	71		

1-Diethylamino-3-butanone (NaOH) — CH₂CH₂COCH₃ ... 82–90

1-Diethylamino-3-butanone (NaOH) — CH₂CH₂COCH₃ ... 51

1-Diethylamino-3-butanone (KOH) — CH₂CH₂COCH₃ ... 51

1-Diethylamino-3-butanone (NaNH₂)

1-Diethylamino-3-butanone (NaNH₂)

1-Diethylamino-3-butanone (KOC₂H₅)

Note: References 206–229 are listed on p. 197.

TABLE VIII—Continued

CARBON ALKYLATIONS WITH METHIODIDES OF β-AMINOKETONES

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cycling Agent	Cyclized Product	Yield %	Reference
1-Diethylamino-3-butanone	[structure, OCH₃, CH₃ (NaNH₂)]	—	—	—	[cyclized structure, OCH₃, CH₃O, H₃C]	43–48	220
	[structure, OCH₃, CH₃O, H₅C₂ (NaNH₂)]	[structure CH₃COCH₂CH₂–, OCH₃, CH₃O, H₅C₂]	—	—	—	—	36
	(large excess NaNH₂)	—	—	—	[cyclized structure, OCH₃, CH₃O, H₅C₂]	—	36
1-Diethylamino-3-butanone	[structure, OCH₃, Cl, CH₃O, H₅C₂ (NaNH₂)]	—	—	—	[cyclized structure, OCH₃, Cl, CH₃O, H₅C₂]	—	36
1-Morpholino-3-butanone	Methyl fluorene-9-carboxylate (NaOCH₃)	[structure, CH₃COCH₂CH₂, CO₂CH₃]	45	*	[cyclized structure, CH₃]	—	227

79	26	
90	26	
84	26	
70	33	
72	33	
31	211	

NaOCH$_3$ — 92

KOH + CH$_3$OH

HCl + CH$_3$CO$_2$H

NaOC$_2$H$_5$ — 29

H$_2$SO$_4$

α-Cyperone

β-Cyperone (stereoisomer of above)

1-Dimethyl-amino-3-butanone   (NaOCH$_3$)

1-Diethylamino-3-pentanone   (NaNH$_2$)

1-Diethylamino-3-pentanone   (NaNH$_2$)

TABLE VIII—*Continued*

CARBON ALKYLATIONS WITH METHIODIDES OF β-AMINOKETONES

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1-Diethylamino-3-pentanone	(NaNH₂) [steroid-type structure with CH₃]	CH₃CH₂COCH₂CH₂— [fused ring structure with CH₃] *or*	23	NaOC₂H₅	[fused ring structure with CH₃ and ketone] *or* [structure with CH₃, H₃C, O]	—	218
1-Morpholino-2-methyl-3-butanone	Ethyl methylacetoacetate (NaOC₂H₅)	—	—	KOH	3,4,6-Trimethyl-2-cyclohexen-1-one	65	32, 32a
1-Morpholino-4-methyl-3-pentanone	Ethyl methylacetoacetate (NaOC₂H₅)	—	—	KOH	3-Isopropyl-6-methyl-2-cyclohexen-1-one (carvenone)	12	32, 32a
1-Morpholino-5-carbethoxy-3-pentanone	Ethyl benzoylbenzoate (NaOC₂H₅)	—	—	—	2-Phenyl-6-keto-1-cyclohexeneacetic acid	—	32
1-Morpholino-4,4-dimethyl-3-pentanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	KOH	3-t-Butyl-2-cyclohexen-1-one	45	32a
1-Morpholino-5-methyl-3-hexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	KOH	3-Isobutyl-2-cyclohexen-1-one	45	32a
1,1-Bis(diethylaminomethyl)acetone	2-Carbethoxycyclohexanone (NaOCH₃)	[structure: O, (CH₂)₄, C, CH₂COCH₃, CH₂, CO₂CH₃]	70	HCl + CH₃CO₂H	[naphthalenol-type structure with OH and CH₃]	15	27a

Reactants	Product	Reagent	Yield (%)	Product	Yield (%)	Ref.	Ref.
1,1-Bis(diethyl-aminomethyl)-acetone 2-Carbethoxycycloheptanone (NaOCH₃)	CH₂=CCOCH₃ / CO₂CH₃ / C(CH₂)₅ / O=C	HCl + CH₃CO₂H	60	OH CH₃ [bicyclic ring]	—	19	27a
1,1-Bis(diethyl-aminomethyl)-acetone 2-Carbethoxycycloheptanone (NaOC₂H₅)	CH₂=CCOCH₃ / CO₂C₂H₅ / C(CH₂)₅ / O=C	—	—	—	—	—	27a
1,1-Bis(diethyl-aminomethyl)-acetone 2-Carbomethoxycyclooctanone (NaOCH₃)	CH₂=CCOCH₃ / CO₂CH₃ / C(CH₂)₆ / O=C	HCl + CH₃CO₂H	63	CH₃ CH₃ / Cl(CH₂)₅ HO / CO₂CH₃	—	35	27a
						51	27a
1,1-Bis(diethyl-aminomethyl)-acetone 2-Carbomethoxycyclononanone (NaOCH₃)	CH₂=CCOCH₃ / CO₂CH₃ / C(CH₂)₇ / O=C	HCl + CH₃CO₂H	68	CH₃ CH₃ / Cl(CH₂)₆ HO / CO₂CH₃	—	42	27a
						37	27a
1,1-Bis(diethyl-aminomethyl)-acetone 2-Carbomethoxycyclotridecanone (NaOCH₃)	CH₂=CCOCH₃ / CO₂CH₃ / C(CH₂)₁₁ / O=C	HCl + CH₃CO₂H	68	CH₃ CH₃ / Cl(CH₂)₁₀ HO / CO₂CH₃	—	50	27a

Note: References 206–229 are listed on p. 197.

TABLE VIII—*Continued*

CARBON ALKYLATIONS WITH METHIODIDES OF β-AMINOKETONES

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
1,1-Bis(diethylamino-methyl)-acetone	2-Carbomethoxycyclopentadecanone (NaOCH₃)		58	HCl + CH₃CO₂H		80	27
1,1-Bis(di-methylamino-methyl)-acetone	(NaOCH₃)		72	KOH + CH₃OH		43	26
				HCl + CH₃CO₂H then (CH₃CO)₂O		76–83	26
1-Methyl-4-piperidone	Diethyl malonate (?)	COCH₂N(CH₃)₂—CH₂CH₂CH(CO₂C₂H₅)₂	25	—	—	—	37
1-Methyl-4-piperidone	Ethyl acetoacetate (KOC₂H₅)	CH₃COCHCO₂C₂H₅—CH₂CH₂COCH₂CH₂N(CH₃)₂	21	H₂SO₄	3-(2′-Dimethylamino)ethyl-δ-car-bethoxy-2-cyclohexen-1-one	—	37
1-Ethyl-4-piperidone	Ethyl acetoacetate (2 moles KOC₂H₅)	[CH₃COCH(CO₂C₂H₅)CH₂CH₂]₂CO	—	—	—	—	37
1-Methyl-4-piperidone	2-Carbethoxycyclopentanone (KOC₂H₅)	(CH₃)₂N(CH₂)₂CO(CH₂)₂	5	HCl		13	37

Amine	Reagent	Product	Yield (%)		Reference
1-Ethyl-4-piperidone	2-Carbethoxycyclohexanone (KOC$_2$H$_6$)		72	—	— — 37
β-Morpholino-propiophenone	Ethyl acetoacetate (NaOC$_2$H$_5$)	3-Phenyl-2-cyclohexen-1-one	— KOH	60	32, 32a
β-Morpholino-propiophenone	COCH$_2$CO$_2$C$_2$H$_5$ CH$_2$CH$_2$CO$_2$C$_2$H$_5$	2-Phenyl-6-keto-1-cyclohexeneacetic acid	—	— — 32	
β-Diethylamino-propiophenone (methosulfate)	Methyl fluorene-9-carboxylate (NaOCH$_3$)	C$_6$H$_5$COCH$_2$CH$_2$ CO$_2$CH$_3$	83	8	— — 227
β-Morpholino-propiophenone (methosulfate)	Methyl fluorene-9-carboxylate (NaOCH$_3$)	C$_6$H$_5$COCH$_2$CH$_2$ CO$_2$CH$_3$	<83	—	— — 227
β-Dimethyl-aminopivalophenone	Sodium cyanide	β-Dimethylaminopivalophenone	50	—	— — 11
2-Dimethylam-inomethyl-cyclohexanone	Diethyl malonate (NaO$_2$H$_5$)	CH$_2$CH(CO$_2$C$_2$H$_6$)$_2$ CH$_2$CH$_2$CO$_2$C$_2$H$_5$	60 ‖	—	— — 215

TABLE VIII—*Continued*

CARBON ALKYLATIONS WITH METHIODIDES OF β-AMINOKETONES

β-Aminoketone as Methiodide	Active Methylene Compound (Condensing Agent)	Simple Alkylation Product	Yield %	Cyclizing Agent	Cyclized Product	Yield %	Reference
2-Diethylaminomethylcyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	2-Keto-Δ^{1,9}-octalin	50	25
2-Dimethylaminomethyl-4-methylcyclohexanone	Diethyl malonate (NaOC₂H₅)	H_3C—[cyclohexanone ring]—$CH_2CH(CO_2C_2H_5)_2$	40	—	—	—	215
		H_3C—[cyclohexanone ring]—$CH_2CH_2CO_2C_2H_5$	28	—	—	—	
2-Dimethylaminomethyl-6-methylcyclohexanone	Diethyl malonate (NaOC₂H₅)	[cyclohexanone ring, CH₃]—$CH_2CH(CO_2C_2H_5)_2$	42 ‖	—	—	—	215
		[cyclohexanone ring, CH₃]—$CH_2CH_2CO_2C_2H_5$					
2-Diethylaminomethyl-6-methylcyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	2-Keto-8-methyl-Δ^{1,9}-octalin	60	25
2-Diethylaminomethyl-4-methoxycyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	—	2-Keto-6-methoxy-Δ^{1,9}-octalin	27	224
2-Diethylaminomethyl-4-methoxycyclohexanone	Ethyl propionylacetate (NaOC₂H₅)	—	—	—	2-Keto-1-methyl-6-methoxy-Δ^{1,9}-octalin	22	221
2-Diethylaminomethyl-4-carbomethoxycyclohexanone	Ethyl propionylacetate (NaOC₂H₅)	—	—	—	2-Keto-1-methyl-6-carbomethoxy-Δ^{1,9}-octalin	13	224

Amine	Reagent			Product	Yield	References
COCH₂CH₂N⟨ (morpholine, on cyclohexene)	Diethyl malonate (NaOC₂H₅)	—	—	4,4-Dicarbethoxy-1-trans-decalone	77	32a
CH(CH₃)₂ cyclohexenone, CH₃, NCH₂⟨(morpholine)	Ethyl methylacetoacetate (NaOC₂H₅)	—	—	(decalone, CH(CH₃)₂, CH₃, HO)	50	32, 228
2-Piperidinomethyl-3-methyl-6-isopropylcyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	KOH	—	2-Keto-5-methyl-8-isopropyl-Δ¹,⁹-octalin	—	32
2-Morpholinomethyl-3-methyl-6-isopropylcyclohexanone	Ethyl acetoacetate (NaOC₂H₅)	—	—	2-Keto-5-methyl-8-isopropyl-Δ¹,⁹-octalin	82	32b
(indanone, NCH₂⟨ morpholine)	Ethyl acetoacetate (NaOC₂H₅)	—	—	C₂H₅O₂C (octahydrophenanthrenone)	40	70
(chromanone, NCH₂⟨ morpholine)	Ethyl acetoacetate (NaOC₂H₅)	—	—	(chromene ketone)	25	229

Note: References 206–229 are listed on p. 197.
* The simple alkylation product was not isolated.
† The simple alkylation product was cyclized as the methyl or isopropyl ether.
‡ The product was isolated as the semicarbazone.
§ The material was cyclized after decarboxylation and reduction to the alcohol.
‖ This is the combined yield of the two products.

TABLE IX

AN ALKYLATION OF INDOLE WITH DIETHYL PIPERIDINOMETHYLFORMAMIDO-MALONATE [53]

$$\text{(indole, NH)} + \text{NCH}_2\text{C(CO}_2\text{C}_2\text{H}_5)_2 \rightarrow$$
$$|$$
$$\text{NHCHO}$$

$$\text{CH}_2\text{C(CO}_2\text{C}_2\text{H}_5)_2 + \text{CH}_2\text{N(piperidine)}$$
$$|$$
$$\text{NHCHO}$$

A   B

Solvent	Catalyst	Yield of Alkylated Product (A) %	Yield of Indole Mannich Base (B) %
Mesitylene	NaOH	10	0
Xylene	NaOH	76	0
Xylene	None	0	70
Toluene	NaOH	21	0
Toluene	None	16	22
Benzene	NaOH	0	13
Benzene	None	0	0

TABLE X

CARBON ALKYLATIONS WITH MANNICH BASES DERIVED FROM NITRO COMPOUNDS [21a]

Mannich Base or Quaternary Salt	Compound Alkylated	Solvent; Catalyst	Product	Yield %
1-Dimethylamino-2-nitro-butane	1-Nitropropane	None; NaOH	3,5-Dinitroheptane	34
1-Diethylamino-2-nitro-butane	1-Nitropropane	None; NaOH	3,5-Dinitroheptane	18
1-Dimethylamino-2-nitro-butane	2-Nitropropane	None; NaOH	2-Methyl-2,4-dinitro-hexane	55
1-Dimethylamino-2-nitro-butane	Methyl cyanoacetate	Xylene; none	Methyl 2-cyano-4-nitro-hexanoate	23
1-Diethylamino-2-nitro-butane	Ethyl cyanoacetate	Xylene; none	Ethyl 2-cyano-4-nitro-hexanoate	16
1-Dimethylamino-2-methyl-2-nitropropane	2-Nitropropane	None; NaOH	Alkylation failed	
1-Dimethylamino-2-methyl-2-nitropropane methiodide	Ethyl acetamido-cyanoacetate	—	Alkylation failed	
1-Dimethylamino-2-methyl-2-nitropropane methiodide	α-Naphthol	—	Alkylation failed	

REFERENCES TO TABLES I–X

[206] Shechter and Kaplan, *J. Am. Chem. Soc.*, **73**, 1883 (1951).

[207] Hansch and Godfrey, *J. Am. Chem. Soc.*, **73**, 3518 (1951); Fox and Bullock, *ibid.*, **73**, 2756 (1951).

[208] Brehm, *J. Am. Chem. Soc.*, **71**, 3541 (1949).

[209] C. Thompson, doctoral thesis, University of Illinois, Urbana, Ill., 1949; Snyder, Thompson, and Hinman, *J. Am. Chem. Soc.*, **74**, 2009 (1952).

[210] Cook, Loudon, and McCloskey, *J. Chem. Soc.*, **1951**, 1203.

[211] McQuillin and Robinson, *J. Chem. Soc.*, **1941**, 586.

[212] Dodson and Sollman, *J. Am. Chem. Soc.*, **73**, 4197 (1951); see also Choudhuri and Mukharji, *J. Ind. Chem. Soc.*, **29**, 336 (1952).

[213] Cope and Hermann, *J. Am. Chem. Soc.*, **72**, 3405 (1950).

[214] Abdullah, *J. Ind. Chem. Soc.*, **12**, 62 (1935).

[215] Frank and Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951).

[216] Hagget and Archer, *J. Am. Chem. Soc.*, **71**, 2255 (1949).

[217] Robinson and Seijo, *J. Chem. Soc.*, **1941**, 582.

[217a] Birch and Murray, *J. Chem. Soc.*, **1951**, 1888.

[218] McQuillin and Robinson, *J. Chem. Soc.*, **1938**, 1097.

[219] Wilds, Ralls, Wildman, and McCaleb, *J. Am. Chem. Soc.*, **72**, 5794 (1950).

[220] Wendler, Slates, and Tishler, *J. Am. Chem. Soc.*, **73**, 3816 (1951).

[221] Shunk and Wilds, *J. Am. Chem. Soc.*, **71**, 3946 (1949).

[222] Birch, Murray, and Smith, *J. Chem. Soc.*, **1951**, 1945.

[223] Robinson and Weygand, *J. Chem. Soc.*, **1941**, 386.

[224] Cook and Robinson, *J. Chem. Soc.*, **1941**, 391.

[225] Cornforth and Robinson, *J. Chem. Soc.*, **1946**, 676.

[226] Grob and Jundt, *Helv. Chim. Acta*, **31**, 1691 (1948).

[227] Stubbs and Tucker, *J. Chem. Soc.*, **1950**, 3288.

[228] Briggs, Gill, Lions, and Taylor, *J. Chem. Soc.*, **1949**, 1098.

[229] Harradence, Hughes, and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1939) [*C. A.*, **33**, 6841 (1939)].

CHAPTER 4

THE VON BRAUN CYANOGEN BROMIDE REACTION

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INTRODUCTION

The reaction of a tertiary amine with cyanogen bromide was first described in 1900 by Julius von Braun,[1] who subsequently elaborated the reaction to such an extent that it rightfully bears his name. The reaction apparently was discovered independently by Scholl and Nörr,[2] whose paper was submitted for publication five weeks after the submission of von Braun's first paper.

Generally, a tertiary amine reacts with cyanogen bromide to yield an alkyl bromide and a disubstituted cyanamide. The direct conversion of

$$\begin{array}{c} R'' \\ \diagdown \\ R'\!-\!N + BrCN \rightarrow RBr + \end{array} \begin{array}{c} R'' \\ \diagdown \\ NCN \\ \diagup \\ R' \end{array}$$
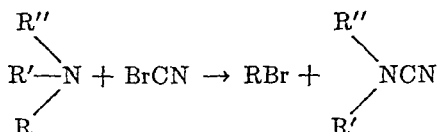
secondary amines to disubstituted cyanamides with cyanogen bromide proceeds in low yield because some of the amine is converted to its hydrobromide. Furthermore, the amine hydrobromide frequently reacts with the cyanamide formed to give a guanidine as the principal product.[3] Preliminary conversion of the secondary amine to a tertiary amine by reaction with formaldehyde, followed by cleavage of the product with cyanogen bromide, affords a better yield of the disubstituted cyanamide.

An acyclic amine yields an alkyl bromide and a disubstituted cyanamide as discrete products. The bromide and cyanamide obtained from the cleavage of a monocyclic amine, such as an N-substituted pyrrolidine,

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[1] von Braun, *Ber.*, **33**, 1438 (1900).
[2] Scholl and Nörr, *Ber.*, **33**, 1550 (1900).
[3] von Braun, *Ber.*, **42**, 2035 (1909).

may be discrete compounds, or they may constitute portions of the same molecule. The product from a bicyclic amine necessarily contains

$$\text{(structure)} \longrightarrow \begin{array}{c} \boxed{} \\ N \\ CN \end{array} + RBr$$

$$\longrightarrow RN(CN)CH_2CH_2CH_2CH_2Br$$
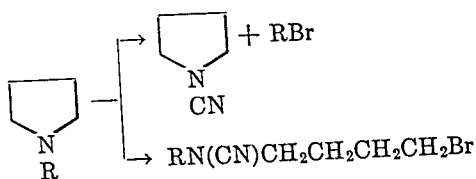
the bromine and the cyanamide group in the same molecule. Nitrogen heterocycles such as pyridine add a mole of cyanogen bromide at the carbon-nitrogen double bond.

$$\text{pyridine} \xrightarrow{\text{BrCN}} \begin{array}{c} \\ N \\ CN \end{array} \begin{array}{c} H \\ \\ Br \end{array}$$
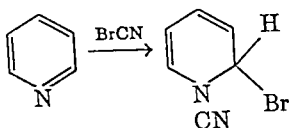
An elimination reaction resulting in the formation of an olefin can occur.[4,5] The presence of a secondary or tertiary alkyl group in the

$$\begin{array}{c} R' \\ \diagdown \\ C(CH_3)NR''R''' \xrightarrow{\text{BrCN}} \\ \diagup \\ R \end{array}$$

$$\begin{array}{c} R' \\ \diagdown \\ C{=}CH_2 + \\ \diagup \\ R \end{array} \begin{array}{c} R''' \\ \diagdown \\ NCN + \\ \diagup \\ R'' \end{array} \begin{array}{c} R' \\ \diagdown \\ C(CH_3)NR''R''' \cdot HBr \\ \diagup \\ R \end{array}$$
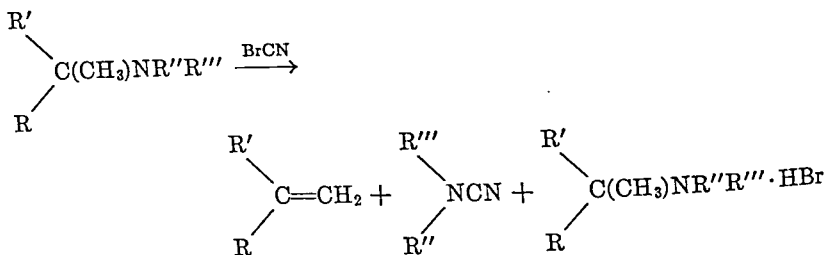
amine is conducive to olefin formation. When the reaction takes this course, a considerable quantity of the amine is converted to the hydrobromide and is thereby prevented from reacting with the cyanogen bromide.

Von Braun[4] early in his work noted differences in the vigor of the reaction of various amines with cyanogen bromide. Simple aliphatic amines react so vigorously that dilution with an inert solvent is required to keep the reaction under control. Derivatives of aniline react less readily; N-alkyldiphenylamines require relatively strenuous conditions for cleavage and give poor yields of products. As the nucleophilic character (basicity) of the nitrogen atom is reduced, its tendency to react with cyanogen bromide is lowered; e.g., N-substituted amides do

[4] von Braun, *Ber.*, **33**, 2728 (1900).
[5] Elderfield and Hageman, *J. Org. Chem.*, **14**, 605 (1949).

not react with cyanogen bromide.[6] The nucleophilic strength of cyanamides is sufficiently low to prohibit reaction with cyanogen bromide.[6] Consequently, when an amine is cleaved by cyanogen bromide, there is no danger of any subsequent reaction between the cyanamides formed and excess cyanogen bromide.

The most thoroughly investigated aspect of the von Braun cyanogen bromide reaction is its use to establish the relative lability of various carbon-nitrogen bonds in tertiary amines. For this purpose it is necessary to determine which of the three substituents is displaced as an alkyl bromide or olefin. Correlation of the large amount of data on the relative ease of removal of different groups enables one to predict approximately how a particular amine will be cleaved (see p. 231 and Table I). Depending upon the structure of the amine, the cleavage may proceed entirely in one direction, or it may give a mixture of all possible alkyl bromides and disubstituted cyanamides.

A serious interfering side reaction involves reaction of the amine with the alkyl bromide produced by the cleavage to form a quaternary ammonium bromide. This side reaction, which is particularly serious when

$$2\ R'{-}\underset{R}{\overset{R''}{N}} + BrCN \rightarrow \left[\underset{R}{\overset{R'}{N(R'')_2}} \right] Br\ * + \underset{R}{\overset{R'}{NCN}}$$
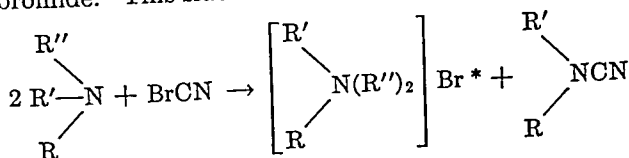
highly reactive bromides are involved, is minimized by making certain that the amine is continually in the presence of excess cyanogen bromide during the reaction.

A survey of the literature discloses surprisingly few cases in which the von Braun cyanogen bromide reaction has been employed for synthetic purposes. It has been applied mainly as a method of degradation in the structural analysis of alkaloids.

Many cleavages, however, when run under the proper experimental conditions, proceed smoothly, and the products are obtained in excellent yields. It appears that the reaction could be applied more widely in synthetic organic chemistry than it has been (see p. 224). Unfortunately, much of the experimental work reported lacks details, particularly with regard to yields, and this may have prevented the reaction from attaining wider synthetic use. Many of the reactions reported to give a mixture of products in low yield could certainly be improved by the proper choice of experimental conditions.

[6] von Braun, *Ber.*, 36, 2286 (1903).
* For convenience, ionic charges will not be shown when it is obvious that the substance represented is a simple quaternary salt.

The material in this chapter is limited to a discussion of the reaction of tertiary * amines with cyanogen bromide. Reactions of cyanogen bromide with other compounds are mentioned only when they add to this general discussion. The effect of the structure of the amine on the direction of cleavage by cyanogen bromide is emphasized.

MECHANISM

Von Braun's observation of the formation of an initial, transient precipitate [1,7] when an amine is mixed with cyanogen bromide led him to propose the preliminary formation of an unstable complex involving quaternary nitrogen. This intermediate is stable only at low temperatures and has never been isolated for characterization.

A brief consideration of the structure and chemical behavior of cyanogen bromide is helpful in understanding its reaction with amines. On the basis of X-ray diffraction studies [8] and Raman spectral data,[9] cyanogen bromide has the structure $Br-C\equiv N$ rather than $Br-\overset{+}{N}\equiv C^-$. In the cyanogen halide series cyanogen chloride nearly always reacts with displacement of the chlorine as chloride ion, whereas in cyanogen iodide the presence of positive iodine is indicated.[10] Cyanogen bromide occupies an intermediate position with respect to the polarity of the carbon-halogen bond. The brominating action of cyanogen bromide [11] and its reaction with Grignard reagents [12] suggest the presence of a positive bromine atom. However, in the greater number of reactions of cyanogen bromide the bromine is displaced as bromide ion. Reaction with aqueous alkali forms bromide and cyanate ions.[10] Reaction with aqueous solutions of primary, secondary, or tertiary amines yields bromide ion quantitatively.[13] The electrolysis of cyanogen bromide in a variety of organic solvents results in migration of bromine to the anode as bromide ion.[14]

The initial reaction of cyanogen bromide with an amine involves a displacement of the bromine as bromide ion with the formation of an

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* Throughout the remainder of this chapter the word "amine" is used to designate a tertiary amine unless otherwise indicated.

[7] von Braun, *Ber.*, **40**, 3914 (1907).

[8] Pauling and Hendricks, *J. Am. Chem. Soc.*, **48**, 641 (1926).

[9] West and Farnsworth, *J. Chem. Phys.*, **1**, 402 (1933).

[10] Kleinberg, *J. Chem. Education*, **23**, 559 (1946).

[11] Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, p. 115, Reinhold Publishing Corp., New York, 1947.

[12] Grignard, Bellet, and Courtot, *Ann. chim.*, [9] **4**, 28 (1915).

[13] Griffith, Jobin, and McKeown, *Trans. Faraday Soc.*, **34**, 316 (1938).

[14] Clark and Streight, *Trans. Roy. Soc. Can.*, [3] **22**, III, 323 (1928) [*C. A.*, **23**, 1824 (1929)].

ionic addition compound in which the nitrogen atom is quaternized. As the terminating step, a nucleophilic displacement by bromide ion removes one of the substituents as an alkyl bromide. Von Braun[4]

$$\left[\begin{array}{c} R'' \\ | \\ R'-NCN \\ | \\ R \end{array} \right]^{+} + Br^{-} \rightarrow \begin{array}{c} R'' \\ \diagdown \\ NCN + RBr \\ \diagup \\ R' \end{array}$$
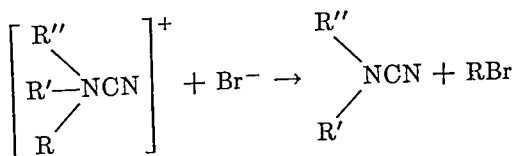
defined the vigor of the reaction as the ease of formation of the quaternary compound. Reduction of the nucleophilic strength of the amine decreases the readiness with which the addition compound is formed. This mechanism is compatible with the known ability of quaternary ammonium salts to function as alkylating agents.[15] The elimination reaction that has been observed [5] when an amine containing a secondary or a tertiary alkyl group is treated with cyanogen bromide can be interpreted in a manner consistent with this mechanism.

No kinetic studies of the von Braun cyanogen bromide reaction have been reported that shed any light on the mechanism under the conditions normally employed. In fact the only recorded kinetic study of the reaction of cyanogen bromide with amines deals with a measurement of the rate of formation of bromide ion in aqueous solution.[13] Although second-order kinetics were observed in aqueous solution, the course of the reaction in this instance is admittedly not identical with that in a non-polar solvent.

Evidence supporting a mechanism involving a second-order displacement by bromide ion is afforded by the observation that those alkyl groups whose halides are known from other studies to react readily in displacement reactions are also most readily cleaved from amines as alkyl bromides.[16]

In this formulation, the von Braun reaction is akin to other reactions of tertiary amines characterized by conversion of the nitrogen to the quaternary state, followed by dealkylation. Some examples follow.

(a) Acetyl bromide reacts [17] with dimethylaniline in much the same manner as does cyanogen bromide. The formation of the disubstituted

$$2C_6H_5N(CH_3)_2 + CH_3COBr \rightarrow [C_6H_5N(CH_3)_3]Br + CH_3CON(CH_3)C_6H_5$$
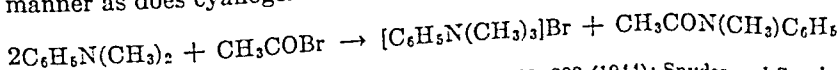
[15] Snyder, Smith, and Stewart, J. Am. Chem. Soc., 66, 200 (1944); Snyder and Speck, ibid., 61, 688, 2895 (1939); Rodinov, Bull. soc. chim. France, 39, 305 (1926); 45, 109 (1929). See also Chapter 3.
[16] von Braun and Engel, Ann., 436, 299 (1924).
[17] Stadel, Ber., 19, 1947 (1886).

acetamide is analogous to the formation of cyanamides by cyanogen bromide; both reactions form methyl bromide which may appear, as above, in a quaternary salt of the amine. Acyl chlorides undergo this reaction far less readily than acyl bromides.

(b) The dealkylation of an amine by a carboxylic acid proceeds much less readily than by an acid halide or anhydride.[18] Heating dimethylaniline to 210–220° with β-phenylpropionic acid gives a 15% yield of the disubstituted amide.[19]

$$C_6H_5N(CH_3)_2 + 2C_6H_5CH_2CH_2CO_2H \xrightarrow{\text{Heat}}$$
$$C_6H_5CH_2CH_2CON(CH_3)C_6H_5 + C_6H_5CH_2CH_2CO_2CH_3$$
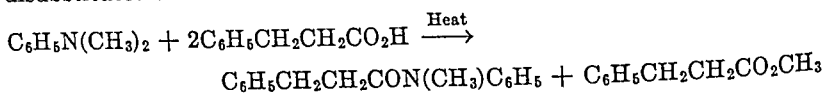
(c) Demethylation of dimethylaniline is effected by heating with n-amyl bromide [20] or phenacyl bromide.[21] These two reactions merely

$$C_6H_5N(CH_3)_2 + n\text{-}C_5H_{11}Br \xrightarrow{150\text{-}160°} C_6H_5N(CH_3)C_5H_{11}\text{-}n + CH_3Br$$

$$C_6H_5N(CH_3)_2 + C_6H_5COCH_2Br \xrightarrow{70°} C_6H_5N(CH_3)CH_2COC_6H_5 + CH_3Br$$
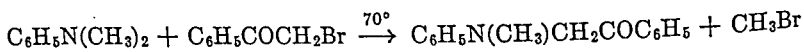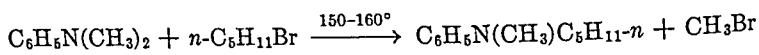
convert one tertiary amine to another; in this respect they differ from the other examples.

Cyanogen bromide reacts with thio ethers and with tertiary phosphines, arsines, and stibines in much the same way as with amines. Thio ethers undergo cleavage with the formation of an alkyl bromide and a thiocyanate,[22,23,24] but no analogous reaction has been observed with

$$RSR' \xrightarrow{\text{BrCN}} RSCN + R'Br$$
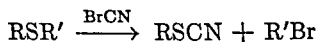
ethers. With thio ethers the relative ease of removal of various alkyl groups parallels closely that observed with amines.

In contrast to triphenylamine, triphenylphosphine forms an addition compound with cyanogen bromide, but no cleavage to bromobenzene takes place. Phosphines appear to be attacked more readily by cyanogen bromide than are amines.[25]
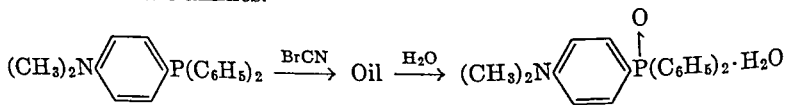
[18] Tiffeneau and Fuhrer, *Bull. soc. chim. France*, [4] **15**, 163 (1914).
[19] von Braun and Weissbach, *Ber.*, **63**, 489 (1930).
[20] Claus and Rautenberg, *Ber.*, **14**, 622 (1881).
[21] Stadel and Siepermann, *Ber.*, **14**, 984 (1881).
[22] von Braun and Engelbertz, *Ber.*, **56**, 1573 (1923).
[23] von Braun, May, and Michaelis, *Ann.*, **490**, 189 (1931).
[24] von Braun and Friedsam, *Ber.*, **63**, 2407 (1930).
[25] Steinkopf and Buckheim, *Ber.*, **54**, 1024 (1921).

Tertiary arsines react with cyanogen bromide [26,27,28] to form addition products that are considerably more stable than those from amines; for example, ethyldiphenylarsine yields an addition complex that can be isolated and undergoes cleavage only when heated.[29] Tertiary stibines [30] react with cyanogen bromide in a similar manner.

$$(C_6H_5)_2AsC_2H_5 \xrightarrow{\text{BrCN}} [(C_6H_5)_2As(CN)C_2H_5]Br \xrightarrow{140°} (C_6H_5)_2AsCN + C_2H_5Br$$
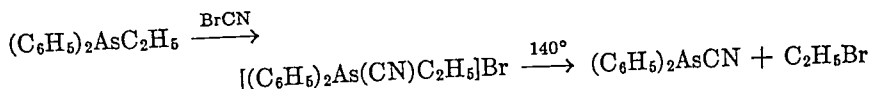
SCOPE AND LIMITATIONS

Acyclic * Amines

The cleavage of an unsymmetrically substituted amine of low molecular weight occurs predominantly in the direction involving displacement of the smallest group.[1] Upon ascending the normal aliphatic series,

$$(n\text{-}C_3H_7)_2NCH_3 \xrightarrow{\text{BrCN}} (n\text{-}C_3H_7)_2NCN + CH_3Br$$

$$(n\text{-}C_3H_7)_2NC_2H_5 \xrightarrow{\text{BrCN}} (n\text{-}C_3H_7)_2NCN + C_2H_5Br$$
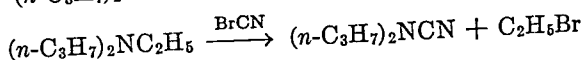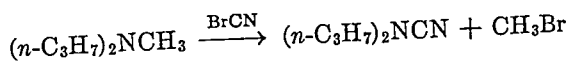
the ease of removal of the alkyl group decreases, the difference between adjacent homologs being greater between the lower members of the series. Above n-hexyl there is no detectable difference in the ease of cleavage of consecutive members.[31] Other structural features, such as branching of the chain and the presence of β,γ-unsaturation, are far more significant than the size of the group. Cleavage of an aromatic amine to give an aryl bromide has never been observed. A rule that is helpful, though not inviolable, for predicting which alkyl group will be removed from the amine can be derived from a comparison of the relative reactivities of the corresponding alkyl bromides. Generally those groups, such as allyl and benzyl, whose halides are known to be highly reactive in displacement reactions [16,32] are cleaved more readily than less reactive groups. However, when a substituent is cleaved with the formation of an olefin, this rule is not applicable.

[26] Steinkopf and Wolfram, *Ber.*, **54**, 848 (1921).
[27] Steinkopf and Schwen, *Ber.*, **54**, 2791 (1921).
[28] Steinkopf and Müller, *Ber.*, **54**, 841 (1921).
[29] Steinkopf, Donat, and Jager, *Ber.*, **55**, 2597 (1922).
[30] Morgan and Yarsley, *Proc. Roy. Soc. London, Series A*, **110**, 534 (1926).
* The term "acyclic" is employed here to denote that the nitrogen atom of the amine is not part of a ring. It is not used in the strict sense that cyclic substituents are excluded.
[31] von Braun and co-workers, *Ann.*, **507**, 1 (1933).
[32] Hammett, *Physical Organic Chemistry*, 1st ed., p. 154, McGraw-Hill Book Co., New York, 1940.

Since a phenyl group is not removed from an amine by cyanogen bromide, dialkylanilines containing different alkyl groups have been employed extensively for dealkylation studies. The n-propyl group is removed more readily than the isopropyl group when n-propylisopropyl-aniline is allowed to react with a molar equivalent of cyanogen bromide

$$C_6H_5N(C_3H_7\text{-}n)C_3H_7\text{-}i \xrightarrow{\text{BrCN}} C_6H_5N(CN)C_3H_7\text{-}i + n\text{-}C_3H_7Br$$
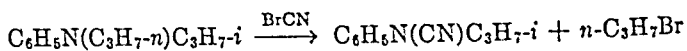
at the temperature of the steam bath.[4] The tendency of the isopropyl group to undergo removal by an elimination reaction has been observed in the reaction of diisopropylaniline with cyanogen bromide. In this reaction an appreciable quantity of diisopropylaniline hydrobromide is formed.[4] Since isopropyl bromide did not react with diisopropylaniline under comparable conditions, it can be concluded that the isopropyl group is removed directly from the quaternary addition compound as propylene.

The greater lability of the n-butyl group compared with the isobutyl group has been shown by the cleavage of n-butylisobutylaniline.[33] Very

$$C_6H_5N(C_4H_9\text{-}n)C_4H_9\text{-}i \xrightarrow{\text{BrCN}} C_6H_5N(CN)C_4H_9\text{-}i + n\text{-}C_4H_9Br$$
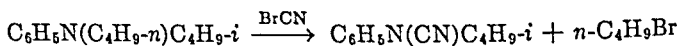
little cleavage to give isobutyl bromide was observed. More remote branching of the chain, as in the isoamyl group and higher homologs, is much less influential.

β,γ-Unsaturation. The labilizing effect of β,γ-unsaturation is demonstrated by the cleavage of methylallylaniline,[4] and diethylcyclopentenyl-amine.[34] No mention was made of the isolation of any cyclopentenyl

$$C_6H_5N(CH_3)CH_2CH{=}CH_2 \xrightarrow{\text{BrCN}} C_6H_5N(CN)CH_3 + CH_2{=}CHCH_2Br$$

$$(C_2H_5)_2NCH\begin{array}{c}CH{=}CH\\ |\\ CH_2{-}CH_2\end{array} \xrightarrow{\text{BrCN}} (C_2H_5)_2NCN + \text{Amine hydrobromide}$$
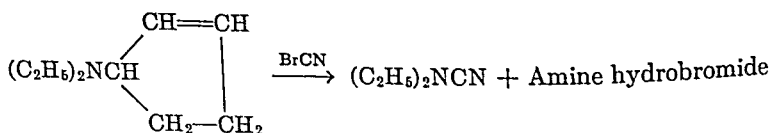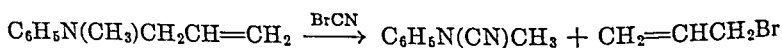
bromide in the latter reaction. It is not surprising that transfer of the unsaturation to a more remote position greatly reduces the lability, as has been shown by the cleavage of dimethyl-4-pentenylamine.[35] This

$$CH_2{=}CH(CH_2)_3N(CH_3)_2 \xrightarrow{\text{BrCN}}$$

$$CH_2{=}CH(CH_2)_3N(CN)CH_3 + [CH_2{=}CH(CH_2)_3N(CH_3)_3]Br$$
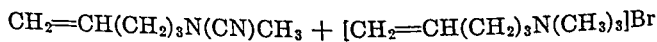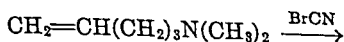
[33] von Braun and Murjahn, *Ber.*, **59**, 1202 (1926).
[34] von Braun and Kühn, *Ber.*, **60**, 2551 (1927).
[35] von Braun and Kohler, *Ber.*, **51**, 79 (1918).

reaction illustrates a common side reaction involving the formation of a quaternary ammonium bromide by the reaction of the liberated alkyl bromide with the amine. A determination of the structure of the quaternary bromide reveals the direction of cleavage of the amine.

Though the benzyl group [36] is more susceptible to cleavage from an amine by cyanogen bromide than the methyl group, a phenethyl group [37]

$$C_6H_5CH_2N(CH_3)C_6H_5 \xrightarrow{BrCN} C_6H_5N(CN)CH_3 + C_6H_5CH_2Br$$

$$C_6H_5CH_2CH_2N(CH_3)C_6H_5 \xrightarrow{BrCN} C_6H_5CH_2CH_2N(CN)C_6H_5 + CH_3Br$$
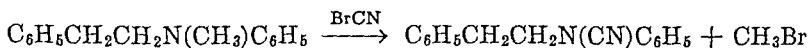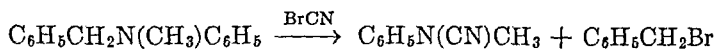
is more resistant to cleavage. When removed further than the β position, the phenyl group exerts no labilizing influence.

The removal of an allyl group in preference to a benzyl group is demonstrated by the cleavage of allyldibenzylamine and allylbenzyl-aniline.[36] In these reactions the products contained only traces of benzyl bromide.

An interesting labilizing effect is associated with the presence of a cyclopropyl group. The cyclopropylmethyl group [38] is more readily removed than a methyl group. It is, however, less readily removed

$$\begin{array}{c} CH_2 \\ / \quad \backslash \\ CH_2 \!-\!\!\!-\! CHCH_2N(CH_3)C_6H_5 \end{array} \xrightarrow{BrCN} C_6H_5N(CN)CH_3 + \begin{array}{c} CH_2 \\ / \quad \backslash \\ CH_2 \!-\!\!\!-\! CHCH_2Br \end{array}$$
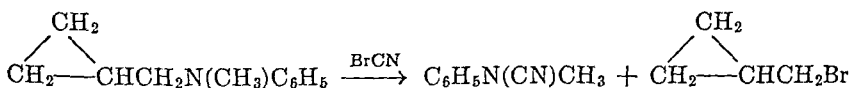
than a benzyl group.

Amines containing the more readily displaced substituents do not necessarily react more vigorously with cyanogen bromide. For instance, tribenzylamine does not react with cyanogen bromide at room temperature; heating to about 70° is required to effect an appreciable rate of reaction.[1]

Substituted Allyl and Benzyl Groups. Extensive studies have been made of the effect of substituents on the ease of removal of allyl [16,39] and benzyl [16,23,24,31,39,40] groups. The introduction of a chlorine or bromine atom into the β or γ position of the allyl group increases the resistance to cleavage to the extent that these groups are less easily removed than a benzyl group.[39] The difference between the effect of bromine and that

$$C_6H_5CH_2N(CH_3)CH_2CBr\!\!=\!\!CH_2 \xrightarrow{BrCN}$$

$$CH_2\!\!=\!\!CBrCH_2N(CN)CH_3 + C_6H_5CH_2Br$$
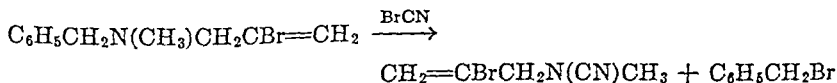
[36] von Braun and Schwartz, *Ber.*, **35**, 1279 (1902).

[37] von Braun, *Ber.*, **43**, 3209 (1910).

[38] von Braun, Fussgänger, and Kühn, *Ann.*, **445**, 201 (1925).

[39] von Braun, Kühn, and Weismantel, *Ann.*, **449**, 249 (1926).

[40] von Braun, Michaelis, and Spanig, *Ber.*, **70**, 1241 (1937).

of chlorine on the lability of substituted allyl groups is too small to be detected by the method of product analysis employed. However, a halogen in the β position has been shown to produce greater resistance to cleavage of the group than one in the γ position.[39] An increase in the lability of the allyl group is caused by a phenyl group in the γ position.[16]

The presence of halogen in the ring of the benzyl group influences the lability of this group in a definite way.[31] With the exception of substitution by fluorine, which appears to exert little influence, the halogen-substituted benzyl groups show greater resistance to cleavage than the unsubstituted benzyl group. The lability of the substituted benzyl group decreases in the order Cl > Br > I.[31] With reference to position,

p-ClC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$Br-p $\xrightarrow{\text{BrCN}}$

$\qquad\qquad$ p-ClC$_6$H$_4$CH$_2$Br + p-BrC$_6$H$_4$CH$_2$N(CN)CH$_3$

m-BrC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$Br-o $\xrightarrow{\text{BrCN}}$

$\qquad\qquad$ m-BrC$_6$H$_4$CH$_2$Br + o-BrC$_6$H$_4$CH$_2$N(CN)CH$_3$
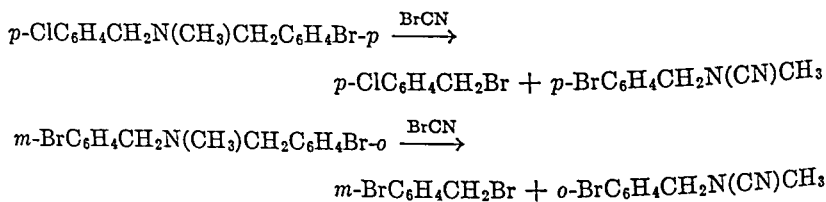
the lability decreases in the order *para* > *meta* > *ortho*. Variation of the position exerts a more pronounced influence than variation of the halogen. This is shown by the cleavage of o-chlorobenzyl-m-iodobenzyl-methylamine.[31] In the examples cited, the occurrence of cleavage almost

m-IC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$Cl-o $\xrightarrow{\text{BrCN}}$

$\qquad\qquad$ m-IC$_6$H$_4$CH$_2$Br + o-ClC$_6$H$_4$CH$_2$N(CN)CH$_3$
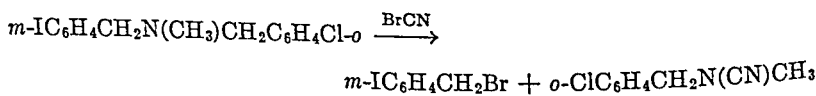
exclusively in the directions indicated shows that the differences in the lability of these substituted benzyl groups are quite pronounced.

Other substituents, like the halogens, decrease the lability of the benzyl group most effectively when in the *ortho* position. Variation of the lability with change in position is not so marked with the nitro group as with the halogens.[40] Qualitative evaluation of the effect of different substituents in any particular position upon increasing the resistance to cleavage of the benzyl group gives the following decreasing order of effectiveness: NO$_2$ > CN > I > Br > Cl > H. The acet-amino group [40] has been shown to increase the resistance to cleavage of the benzyl group to a greater extent than chlorine but no data comparing it with bromine and iodine are available. The nitro and cyano groups

p-CH$_3$CONHC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$Cl-p $\xrightarrow{\text{BrCN}}$

$\qquad\qquad$ p-CH$_3$CONHC$_6$H$_4$CH$_2$N(CN)CH$_3$ + p-ClC$_6$H$_4$CH$_2$Br
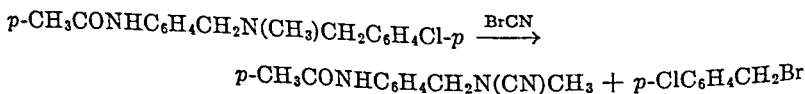
increase the resistance to cleavage of a benzyl group to a greater extent than any of the halogens, even when the latter are in the *ortho* position.[40]

$$p\text{-}O_2NC_6H_4CH_2N(CH_3)CH_2C_6H_4Cl\text{-}o \xrightarrow{\text{BrCN}}$$

$$p\text{-}O_2NC_6H_4CH_2N(CN)CH_3 + o\text{-}ClC_6H_4CH_2Br$$

$$p\text{-}NCC_6H_4CH_2N(CH_3)CH_2C_6H_4I\text{-}o \xrightarrow{\text{BrCN}}$$

$$p\text{-}NCC_6H_4CH_2N(CN)CH_3 + o\text{-}IC_6H_4CH_2Br$$
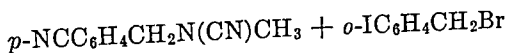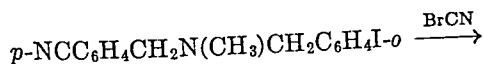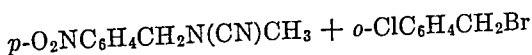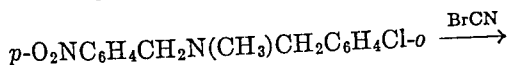
However, no case has been reported in which the lability of a benzyl group has been reduced by a substituent on the ring to the extent that its resistance to cleavage equals that of a methyl group.

Substituents that labilize the benzyl group, listed in the order of decreasing effectiveness, are as follows: methoxyl > phenyl, cyclohexyl > *p*-xenyl > ethyl > methyl > H.[23,31] In this series also, a substituent in the *ortho* position produces a less labile benzyl group than when it is in the *meta* or *para* position. Though a methyl group in the *para* position labilizes the benzyl group, a methyl group in the *ortho* position does not.[23] However, the *o*-methylbenzyl group is more labile than the *p*-chloro-

$$o\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2C_6H_5 \xrightarrow{\text{BrCN}}$$

$$C_6H_5CH_2Br + o\text{-}CH_3C_6H_4CH_2N(CN)CH_3$$
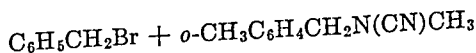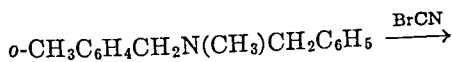
benzyl group.[31] The *p*-methoxybenzyl group is the most labile of those

$$o\text{-}CH_3C_6H_4CH_3N(CH_3)CH_2C_6H_4Cl\text{-}p \xrightarrow{\text{BrCN}}$$

$$p\text{-}ClC_6H_4CH_2N(CN)CH_3 + o\text{-}CH_3C_6H_4CH_2Br$$
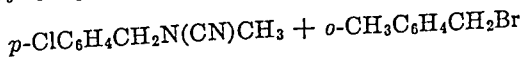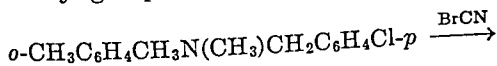
studied;[23] no data are available permitting a direct comparison of it with the allyl group.

In a study of the relative ease of cleavage of amines containing substituted benzyl groups, von Braun and Engel[16] observed a close relationship between the ease of cleavage and the rate with which similarly substituted benzyl chlorides react with ethoxide ion. In the accompanying table are given some second-order rate constants for the reaction of several benzyl chlorides with ethoxide ion as determined by the method of Franzen.[41] The increase in ease of removal of these benzyl groups from an amine by cyanogen bromide parallels the increase in these rate constants.

[41] Franzen, *J. prakt. Chem.*, [2] 97, 61 (1918).

RELATIVE REACTIVITIES OF SOME BENZYL CHLORIDES WITH ETHOXIDE ION

Chloride	k_2
Benzyl	7.9 ± 0.3
p-Methylbenzyl	11.9 ± 0.3
p-Ethylbenzyl	14.9 ± 0.8
p-Phenylbenzyl	73.8 ± 0.2

Though the allyl group is more labile than the benzyl group, introduction of some labilizing groups into the *para* position of the benzyl group causes a greater increase in lability than introduction of the same groups into the γ position of the allyl group. This is shown by the accompanying reactions,[16] for which only the major products are given.

$$p\text{-RC}_6\text{H}_4\text{CH}_2\text{N(CH}_3)\text{CH}_2\text{CH}{=}\text{CHR} \xrightarrow{\text{BrCN}}$$
$$\text{R} = \text{C}_6\text{H}_5 \text{ or CH}_3$$

$$\text{RCH}{=}\text{CHCH}_2\text{N(CN)CH}_3 + p\text{-RC}_6\text{H}_4\text{CH}_2\text{Br}$$
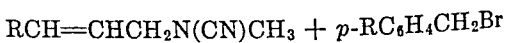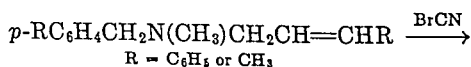
The effect of structure on the ease of cleavage of various substituted allyl and benzyl groups is closely analogous to the effect on the reactivities of the corresponding allyl and benzyl halides in second-order displacement reactions. For example, those substituents that have been shown to increase the ease of cleavage of the benzyl group from an amine by cyanogen bromide also increase the reactivity of the benzyl halides in displacement reactions.

The Cyanomethyl Group. The ease of cleavage of the cyanomethyl group [42] has been estimated to be approximately equal to that of the ethyl group. Diethylaminoacetonitrile undergoes cleavage in both directions in nearly equal amounts. Similar behavior is exhibited by the

$$(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CN} \xrightarrow{\text{BrCN}} \begin{array}{l} \to \text{C}_2\text{H}_5\text{N(CN)CH}_2\text{CN} + \text{C}_2\text{H}_5\text{Br} \\ \to (\text{C}_2\text{H}_5)_2\text{NCN} + \text{BrCH}_2\text{CN} \end{array}$$
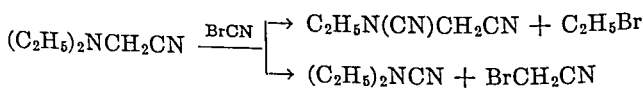
carbethoxymethyl group. Cleavage of dimethylaminoacetonitrile proceeds nearly completely in the direction yielding methyl bromide. The cyanomethyl group reduces the ease with which an amine will react with cyanogen bromide. When methylanilinoacetonitrile is treated with cyanogen bromide at 100° for five hours, bromination of the ring occurs in preference to cleavage of the amine.[43] No reaction takes place at room temperature.

$$\text{C}_6\text{H}_5\text{N(CH}_3)\text{CH}_2\text{CN} \xrightarrow[100°]{\text{BrCN}} p\text{-BrC}_6\text{H}_4\text{N(CH}_3)\text{CH}_2\text{CN}$$
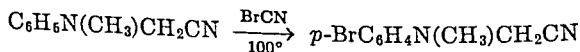
[42] von Braun, *Ber.*, **40**, 3933 (1907).
[43] von Braun, *Ber.*, **41**, 2100 (1908).

Methylenediamines. The methylenic linkage in tetrasubstituted methylenediamines is cleaved by cyanogen bromide with extreme ease.[44]

$$[(C_6H_5CH_2)_2N]_2CH_2 \xrightarrow{2BrCN} 2(C_6H_5CH_2)_2NCN + CH_2Br_2$$
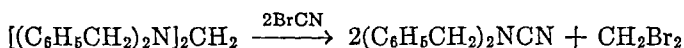
Even when the labile benzyl group is present, cleavage proceeds exclusively in the direction shown.[3]

A Steric Anomaly. A peculiar steric effect involving the reaction of some *ortho*-substituted aromatic amines has been observed.[45,46] Some diphenylmethane derivatives containing two dimethylamino groups both of which are hindered by a group in the *ortho* position, e.g., I and II,
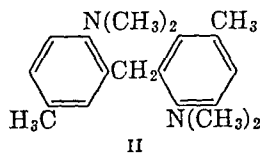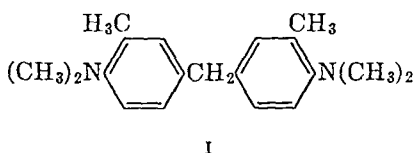
undergo no reaction with cyanogen bromide. Attributing this lack of reactivity to a steric or *ortho* effect, one would predict that compounds of a similar type containing one hindered and one unhindered dimethylamino group, e.g., III and IV, would react only at the unhindered group. However, under the same conditions these compounds react at both dimethylamino groups.[45] A similar situation has been observed when
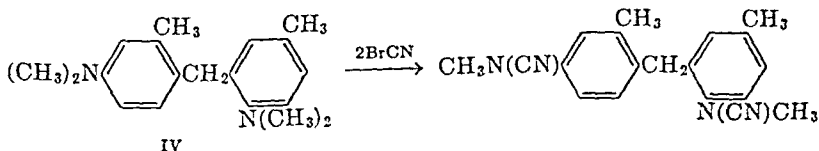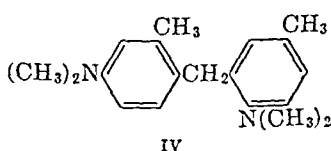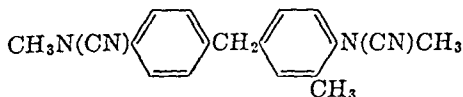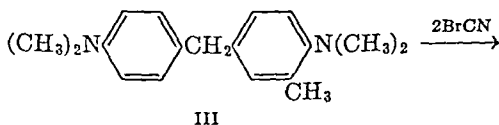
these compounds were treated with iodoacetonitrile. Analogous compounds in the biphenyl series give the same results.[46] No satisfactory explanation of this anomaly has been offered.

[44] von Braun and Röver, *Ber.*, **36**, 1196 (1903).
[45] von Braun and Kruber, *Ber.*, **46**, 3470 (1913).
[46] von Braun and Mintz, *Ber.*, **50**, 1651 (1917).

CYCLIC AMINES

An aspect of the reaction of nitrogen ring compounds with cyanogen bromide that has received considerable study is the determination of the relative ease of fission of various ring systems. In the method most frequently employed, the ratios of ring cleavage to dealkylation of different rings containing the same alkyl group as a substituent on the nitrogen atom are compared. From a knowledge of the relative ease of displacement of several of the alkyl groups discussed previously, it is frequently possible to select a substituent that permits either complete dealkylation or complete cleavage of the ring.

Ethylenimines. Ethylenimines are known to undergo ring cleavage very readily in the presence of electrophilic reagents, i.e., compounds that convert the amino nitrogen to the quaternary state. Therefore, it is not surprising that this ring system is readily cleaved by cyanogen bromide. Only four examples of the reaction of 1-substituted ethylenimines with cyanogen bromide have been reported.[5] By the gradual addition of 1-ethyl- or 1-n-butyl-ethylenimine to an ether solution of cyanogen bromide, there are obtained 88% and 94% yields, respectively, of the β-bromoethylcyanamides. The ring system in ethylenimines is so labile that it is doubtful if any substituent could be displaced from the

$$\begin{array}{c} CH_2\!\!-\!\!-\!\!CH_2 \\ \diagdown \quad \diagup \\ N \\ | \\ R \end{array} \xrightarrow{BrCN} BrCH_2CH_2N(CN)R$$

$$R = C_2H_5 \text{ or } n\text{-}C_4H_9$$
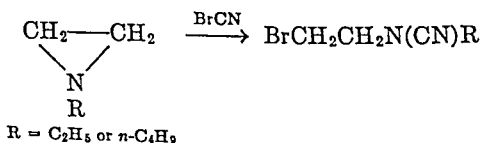
nitrogen without cleaving the ring.

Cleavage of symmetrical rings of the type shown above can yield only one bromoalkyl cyanamide. An unsymmetrical cyclic structure offers the possibility of cleavage in two directions. Only a few examples of the unsymmetrical type have been reported.[5] Three products were obtained from the reaction of 1-n-butyl-2-ethylethylenimine with cyanogen bromide in ether solution. This cleavage at the secondary alkyl linkage

$$\begin{array}{c} H_5C_2CH\!\!-\!\!-\!\!CH_2 \\ \diagdown \quad \diagup \\ N \\ | \\ C_4H_9\text{-}n \end{array} \xrightarrow{BrCN} \underset{82\%}{C_2H_5CHBrCH_2N(CN)C_4H_9\text{-}n}$$

$$+ \underset{11\%}{CH_3CH\!\!=\!\!CHCH_2N(CN)C_4H_9\text{-}n} + \underset{6\%}{C_2H_5CH(NHC_4H_9\text{-}n)CH_2Br \cdot HBr}$$
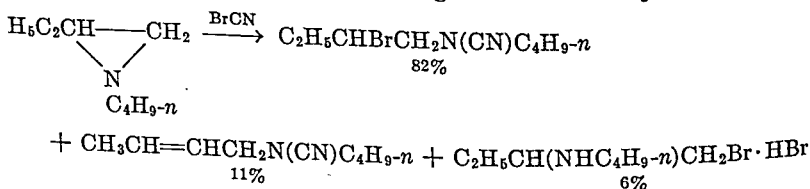
rather than at the primary alkyl linkage is inconsistent with the greater ease of cleavage of the n-propyl group compared to the isopropyl group

(see p. 206) and the direction of cleavage of 1-*n*-butyl-2-methylpyrrolidine (see p. 214). The greater strain in the ethylenimine ring may account for this difference.

The reaction of 1-*n*-butyl-2,2-dimethylethylenimine [5] with cyanogen bromide yields a considerable quantity of an unidentified polymeric material. The only discrete products isolated are those shown in the

$$(CH_3)_2C\text{------}CH_2 \xrightarrow{\text{BrCN}}$$
$$\diagdown \quad \diagup$$
$$N$$
$$C_4H_9\text{-}n$$

$$CH_2\text{==}C(CH_3)CH_2N(CN)C_4H_9\text{-}n + (CH_3)_2CBrCH_2NHC_4H_9\text{-}n\cdot HBr$$
$$\quad\quad\quad 29\% \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad 16\%$$
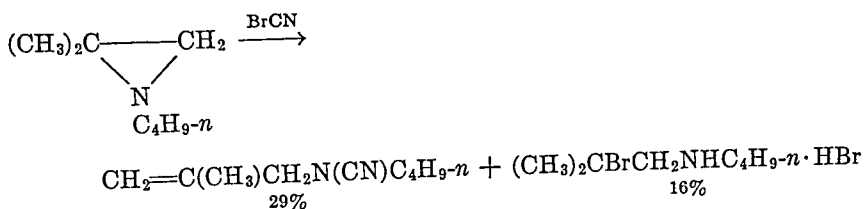
accompanying formulation. These results show that ring cleavage occurs preferentially at the tertiary alkyl linkage by an elimination reaction. The hydrogen bromide produced accounts for the observed formation of polymeric material.

Azetidines. The only azetidine whose reaction with cyanogen bromide has been reported is 1-*n*-butylazetidine.[5]

$$\quad\quad CH_2$$
$$\quad\diagup\quad\diagdown$$
$$CH_2 \quad CH_2 \xrightarrow{\text{BrCN}} Br(CH_2)_3N(CN)C_4H_9\text{-}n$$
$$\quad\diagdown\quad\diagup \quad\quad\quad\quad\quad 85\%$$
$$\quad\quad N$$
$$\quad\quad C_4H_9\text{-}n$$
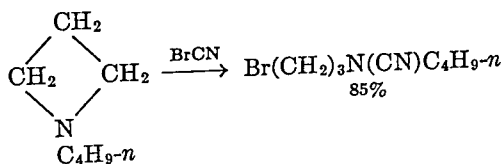
Pyrrolidines and Other Five-Membered Rings. Simple pyrrolidines are considerably more resistant to ring cleavage than are ethylenimines. Varying degrees of stability are observed in related compounds such as dihydroindoles, dihydroisoindoles, and indolizidines.

When treated with cyanogen bromide in benzene solution, 1-*n*-butylpyrrolidine gives a quantitative yield of *n*-butyl-δ-bromobutylcyanamide.[5,47] Even when the more labile ethyl group is employed as the

$$\text{[pyrrolidine ring]} \xrightarrow{\text{BrCN}} Br(CH_2)_4N(CN)C_4H_9\text{-}n$$
$$\quad\quad N$$
$$\quad\quad C_4H_9\text{-}n$$
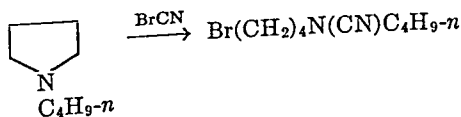
substituent, the ring is cleaved to the extent of 94%.[48] However, when a benzyl group is employed as the substituent, the pyrrolidine ring is not

[47] Ochiai, Tsuda, and Yokoyama, *Ber.*, **68**, 2291 (1935).
[48] von Braun, *Ber.*, **44**, 1252 (1911).

opened.[49]   A few unsymmetrical pyrrolidines undergo ring cleavage in

$$\underset{\substack{\text{N}\\ \text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2\text{-}o}}{\boxed{}} \xrightarrow{\text{BrCN}} \underset{\substack{\text{N}\\ \text{CN}}}{\boxed{}} + o\text{-CH}_2=\text{CHC}_6\text{H}_4\text{CH}_2\text{Br}$$
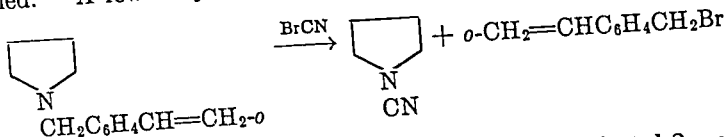
both possible directions.   The ring opening of 1-*n*-butyl-2-methyl-pyrrolidine proceeds predominantly to yield the primary alkyl bromide.[5]

$$\underset{\substack{\text{N}\\ \text{C}_4\text{H}_9\text{-}n}}{\boxed{}}\text{CH}_3 \xrightarrow{\text{BrCN}}$$

$$\underset{70\%}{\text{Br(CH}_2)_3\text{CH(CH}_3)\text{N(CN)C}_4\text{H}_9\text{-}n} + \underset{26\%}{\text{CH}_3\text{CHBr(CH}_2)_3\text{N(CN)C}_4\text{H}_9\text{-}n}$$
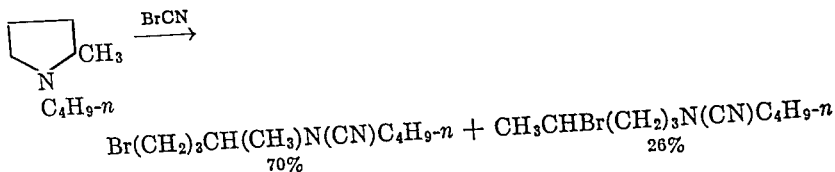
When the isopropyl group is present instead of the *n*-butyl group, cleavage still gives predominantly the primary bromide, but the 1-phenyl analog[50] cleaves to yield the secondary bromide as the major product.

Reaction of 1-*n*-butyl-2,2-dimethylpyrrolidine with cyanogen bromide proceeds exclusively by cleavage at the tertiary alkyl linkage.[5]   This

$$\underset{\substack{\text{N}\\ \text{C}_4\text{H}_9\text{-}n}}{\boxed{}}\text{(CH}_3)_2 \xrightarrow{\text{BrCN}} \left[\underset{\substack{\text{N}\\ \text{H} \quad \text{C}_4\text{H}_9\text{-}n}}{\boxed{}}\text{(CH}_3)_2\right]\text{Br}$$
$$\underset{42\%}{}$$

$$+ \underset{41\%}{\text{CH}_2=\text{C(CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{N(CN)C}_4\text{H}_9\text{-}n}$$
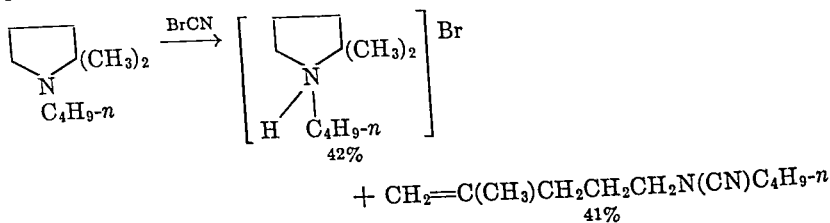
mode of cleavage, which is analogous to that of the similarly substituted ethylenimine (see p. 213), indicates that cyanogen bromide removes a tertiary alkyl group from an amine by an elimination reaction more readily than it removes a simple primary alkyl group by a displacement reaction.   Compared with the pyrrolidine ring, the dihydroindole ring is slightly more susceptible to cleavage.[51]

$$\underset{\substack{\text{N}\\ \text{CH}_3}}{\text{dihydroindole}} \xrightarrow{\text{BrCN}} \underset{40\%}{\underset{\text{N(CN)CH}_3}{\text{CH}_2\text{CH}_2\text{Br}}} + \underset{27\%}{\underset{\substack{\text{N}\\ \text{CN}}}{\text{indoline}}}$$
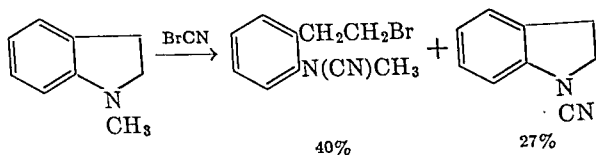
[49] von Braun, *Ber.*, **49**, 2629 (1916).
[50] Elderfield and Green, *J. Org. Chem.*, **17**, 431 (1952).
[51] von Braun, *Ber.*, **51**, 96 (1918).

The ring system in dihydroisoindoles contains carbon-nitrogen bonds of the benzyl type; dihydroisoindoles are, accordingly, more susceptible to ring fission than dihydroindoles. The ring is sufficiently stable, however, to permit the removal of a benzyl group without cleavage of the ring, as shown by the accompanying equation.[52]

$$C_6H_5CH_2N \quad \text{[structure]} \quad NCH_2C_6H_5 \xrightarrow{2BrCN} NCN \quad \text{[structure]} \quad NCN$$

97%

$$+$$

$$2C_6H_5CH_2Br$$
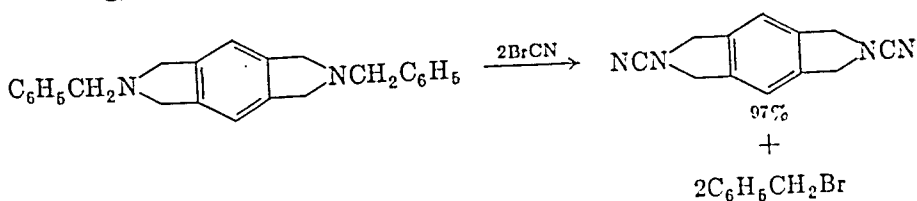
When the substituent on the nitrogen of a dihydroisoindole is a methyl group, ring opening occurs more readily than demethylation.[53]

Piperidines and Other Six-Membered Rings. A direct comparison of the relative stability of the piperidine and pyrrolidine rings is afforded by the reaction of indolizidine [54] with cyanogen bromide. The direction of ring cleavage was determined by degradation of the reaction product to racemic coniine. Though 1-ethylpyrrolidine undergoes nearly

$$\text{[indolizidine structure]} \xrightarrow{BrCN} \text{[structure]} N-CH_2CH_2CH_2Br$$
$$\qquad\qquad\qquad\qquad\qquad CN$$
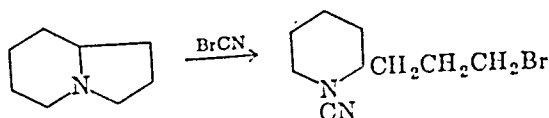
complete ring cleavage, 1-ethylpiperidine undergoes de-ethylation to the extent of 66%.[48] The ease of cleavage of the piperidine ring is roughly equal to the ease of removal of the n-propyl group as shown by the reaction of 1-n-propylpiperidine [48] with cyanogen bromide. Benzyl

$$\text{[structure]} \xrightarrow{BrCN} \text{[structure]} + Br(CH_2)_5N(CN)C_3H_7\text{-}n$$
$$C_3H_7\text{-}n \qquad\qquad CN$$
$$\qquad\qquad 40\% \qquad\qquad 60\%$$
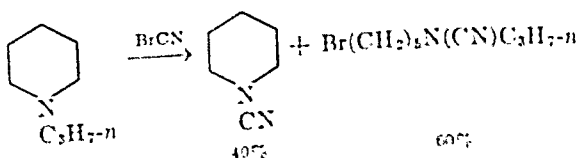
groups can be removed with no detectable cleavage of the piperidine ring.[48,49]

An excellent example of an elimination reaction is furnished by the behavior of ethyl β-(1-piperidyl)propionate.[3] This is the only reported example of the reaction of a β-amino acid ester with cyanogen bromide.

piperidine-$CH_2CH_2CO_2C_2H_5$ $\xrightarrow{\text{BrCN}}$ piperidine-$CH_2CH_2CO_2C_2H_5 \cdot HBr$ (43%) + piperidine-CN + $CH_2{=}CHCO_2C_2H_5$
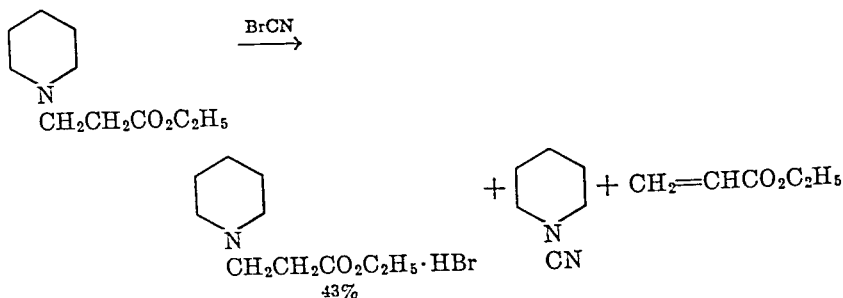
To insure that cleavage of the piperidine ring will be predominant, the substituent should possess a resistance to cleavage equal to or greater than that of the n-butyl group. Surprisingly, 1-isopropyl-4-pipecoline is reported[56] to undergo dealkylation with no detectable ring cleavage. The reaction of 1-phenylpiperidine[7,57] can result only in ring opening since the phenyl group cannot be displaced.

Tropane, which contains both the piperidine and pyrrolidine ring systems, is completely demethylated by cyanogen bromide. Under the

tropane-NCH_3 $\xrightarrow{\text{BrCN}}$ tropane-NCN + [tropane-$N(CH_3)_2$]Br
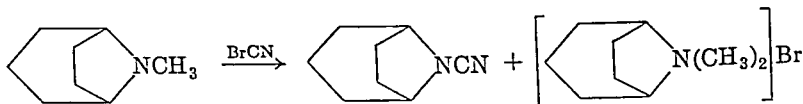
conditions employed for this reaction, nearly half the tropane was converted to the quaternary salt by reaction with the methyl bromide formed.[48]

Tetrahydroquinoline is slightly more resistant to ring cleavage than piperidine. For 1-n-propylpiperidine[48] the ratio of ring opening to depropylation is 3:2; for 1-n-propyltetrahydroquinoline[58] this ratio is 3:4. The contrasting modes of reaction of 1-methyl-3-phenyltetrahydroquinoline and 1-methyl-2-phenyltetrahydroquinoline show how the stability of the ring can be modified. From the former the only product isolated was 1-cyano-3-phenyltetrahydroquinoline, whereas from the latter there resulted a 50% yield of the ring-opened product.[59]

[56] Elderfield, Pitt, and Wempen, J. Am. Chem. Soc., 72, 1344 (1950).
[57] von Braun, Ber., 41, 2165 (1908).
[58] von Braun, Ber., 42, 2219 (1909).
[59] von Braun, Seemann, and Schultheis, Ber., 55, 3803 (1922).

goes ring opening with no appreciable demethylation, the *o*-ethylbenzyl group is removed in preference to cleavage of the ring.[62]

$$\xrightarrow{\text{BrCN}} o\text{-}C_2H_5C_6H_4CH_2Br +$$
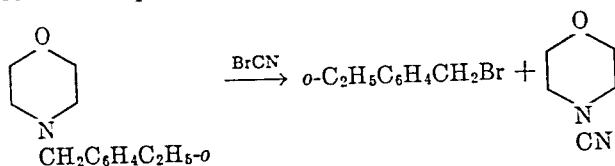
In benzomorpholine the ring is considerably more stable than in morpholine. Reaction of 4-methylbenzomorpholine with cyanogen bromide results in recovery of half of the starting material; no product
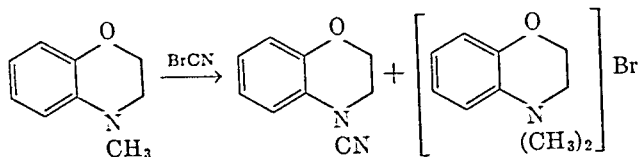
resulting from ring opening is obtained.[63]

The piperazine ring is the most readily cleaved of the six-membered rings that have been studied. When cyanogen bromide is added to 1,4-dimethylpiperazine, the major products isolated are the hydro-

$$H_3CN \underbrace{\qquad} NCH_3 \cdot 2HBr + 2CH_2{=}CHN(CN)CH_3$$
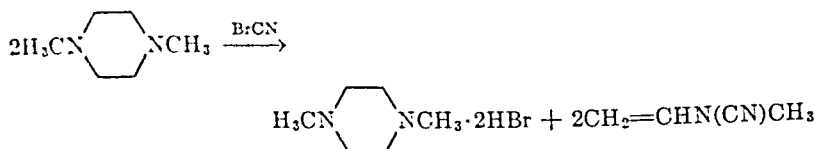
bromide of the starting material and methylvinylcyanamide.[64]

Pyridines and Quinolines. Reaction of γ-dipyridyl in absolute ethanol with two moles of cyanogen bromide gives an adduct whose composition corresponds to the addition of one mole of cyanogen bromide.[65] This is one of the few adducts of this type to have been isolated
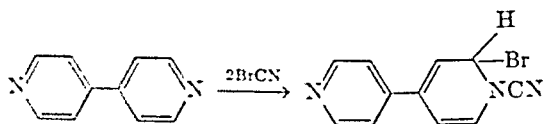
and characterized. Reaction of pyridine with cyanogen bromide, followed by treatment with a primary or secondary amine, gives products

believed to result from the intermediate formation of 1-cyano-2-bromo-1,2-dihydropyridine.[66]   Quinoline reacts with cyanogen bromide in
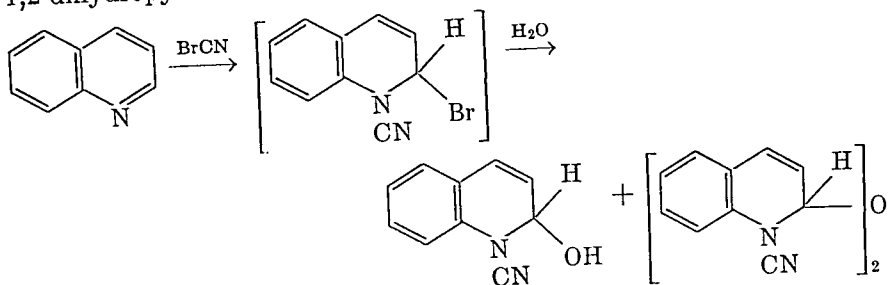
moist ether to give 1-cyano-2-hydroxy-1,2-dihydroquinoline and its ether.[67, 68, 69]

Simultaneous reaction of quinoline with cyanogen bromide and anhydrous hydrogen cyanide in benzene at 0° yields 1,2-dicyano-1,2-di-

hydroquinoline.[68, 70]   If the quinoline ring contains substituents in the 2 or 8 position, this reaction takes place less readily and it is necessary to operate in sealed tubes at 150°.   The structures of these products
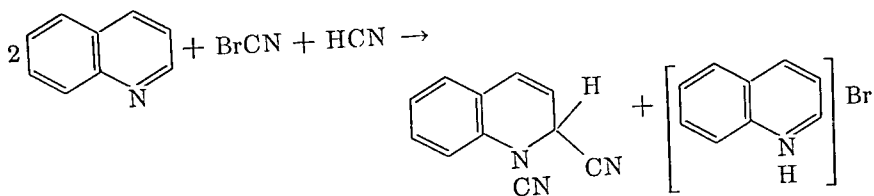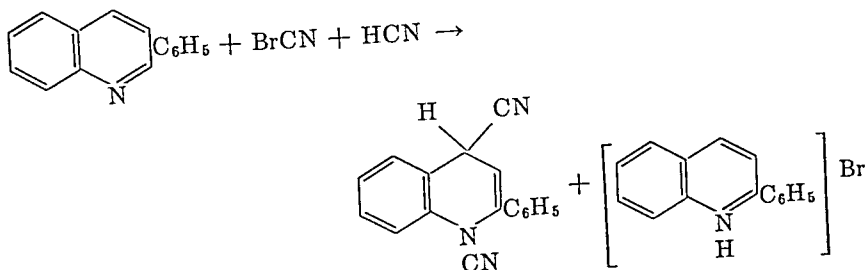
were established by conversion to the quinolinecarboxylic acids.

[66] Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, p. 110, Reinhold Publishing Corp., New York, 1947.

[67] Shimidzu, *J. Pharm. Soc. Japan*, **529**, 243 (1926) [*C. A.*, **20**, 2680 (1926)].

[68] Mumm and Ludwig, *Ann.*, **514**, 34 (1934).

[69] von Braun, *Wallach-Festschrift*, 313 [*C. A.*, **5**, 888 (1911)].

[70] Mumm and Herrendorfer, *Ber.*, **47**, 758 (1914).

Alkaloids

The von Braun cyanogen bromide reaction has frequently been employed in the degradation of alkaloids by attack at the basic nitrogen atoms. Its importance in this field is comparable to that of the classical Hofmann and Emde methods of degradation. Another reaction bearing von Braun's name, which also has found considerable application as a method of degradation, consists in dealkylation of secondary amines by preparing the benzoyl derivative and treating this amide with phosphorus pentachloride or bromide.

A few examples of the reaction of cyanogen bromide with alkaloids are presented merely to indicate the applicability of the reaction in this field. No detailed coverage or critical evaluation in relation to other methods of degradation [71] is intended.

The value of any reaction to be used as a method of degrading compounds of unknown structure is greatly enhanced by a thorough understanding of the course of the reaction when applied to many simple compounds of known structure. The examples discussed above have aided in the development of this reaction as a method of degradation.

Though repeated application of Hofmann's method of exhaustive methylation often effects complete removal of a nitrogen atom, originally part of a heterocyclic ring, this cannot be accomplished by the use of cyanogen bromide. On the other hand, cyanogen bromide will sometimes effect ring opening where the Hofmann method fails, namely, in the dihydroindole and tetrahydroquinoline ring systems.[49] Hydrocotarnine (VI) provides an example of the degradation of a compound in different ways by the Hofmann and von Braun methods.[61, 72] This example also illustrates some of the deductions that can be made from the reaction of a compound with cyanogen bromide. Analysis of the
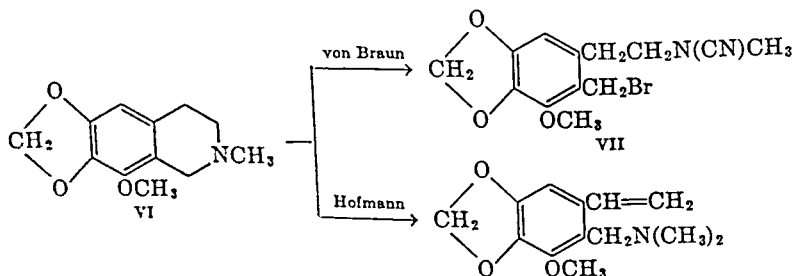
[71] Houben, *Die Methoden der organischen Chemie*, 2nd ed., Vol. IV, pp. 519–526, G. Thieme, Leipzig, 1924.

[72] Small, in Gilman, *Organic Chemistry*, Vol. II, 2nd ed., p. 1175, John Wiley & Sons, New York, 1943.

reaction product VII, showing that the elements of cyanogen bromide have been added, implies that a tertiary amine nitrogen atom constitutes part of a ring that has undergone opening. Once the presence of an N-methyl group has been established, it can be concluded that the nitrogen ring system is one that is sufficiently labile to undergo ring cleavage in preference to demethylation. This indicates that a stable ring of the piperidine or tetrahydroquinoline type is probably not involved. The observed behavior, however, is compatible with ring systems such as dihydroindole, dihydroisoindole, or tetrahydroisoquinoline. A selection among these possibilities will be dictated by other consistent experimental data.

Conessine (VIII), whose structure is not known, reacts with one equivalent of cyanogen bromide in ether solution to give two principal products.[73] One of these (IX), which proved to be a quaternary ammonium salt, is doubtless formed by the reaction of two moles of methyl bromide with the starting material. The other (X) has the composition
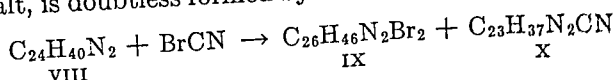
$$\underset{\text{VIII}}{C_{24}H_{40}N_2} + BrCN \rightarrow \underset{\text{IX}}{C_{26}H_{46}N_2Br_2} + \underset{\text{X}}{C_{23}H_{37}N_2CN}$$

of a cyanamide arising from a demethylation of conessine. Further treatment of the cyanamide X with cyanogen bromide yields a product

$$\underset{\text{X}}{C_{23}H_{37}N_2CN} + BrCN \rightarrow \underset{\text{XI}}{C_{22}H_{34}N_2(CN)_2}$$
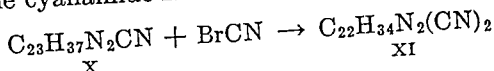
(XI) arising from a second demethylation. These results strongly indicate that each of the nitrogen atoms in conessine contains at least one methyl group. Furthermore, these amine functions must be joined to the molecule by bonds more stable with respect to cleavage by cyanogen bromide than the N-methyl bond.

An interesting application of the cyanogen bromide reaction to the morphine alkaloids is the comparison of the behavior of diacetylmorphine (XII), which undergoes demethylation, with that of thebaine (XIV), which adds the elements of cyanogen bromide.[74]
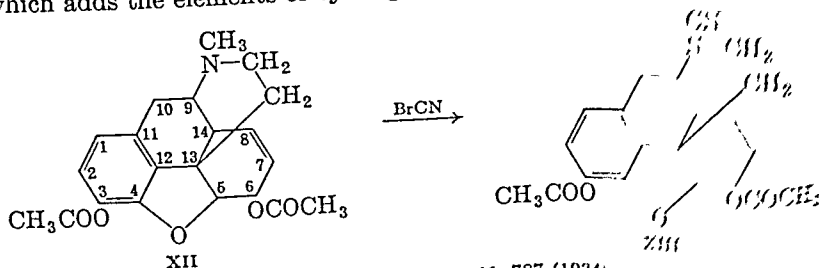
XII

[73] Siddiqui and Siddiqui, *J. Indian Chem. Soc.*, **11**, 787 (1934).
[74] von Braun, Kruber, and Aust, *Ber.*, **47**, 2312 (1914).
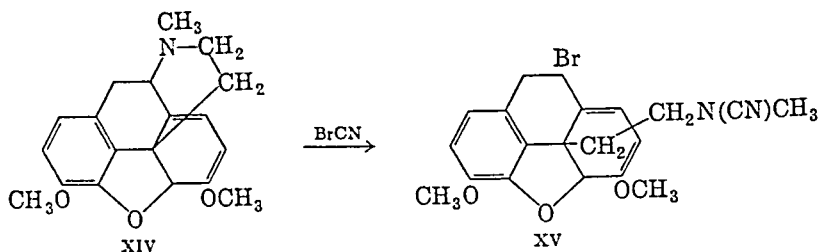
The only pertinent structural difference in the nitrogen ring system of these two compounds is the presence of β,γ unsaturation between carbon atoms 8 and 14 in thebaine (XIV) in contrast to the more remote γ,δ unsaturation at the 7–8 position in diacetylmorphine (XII). The β,γ-double bond in position 8–14 involves an allylic linkage to the nitrogen atom which labilizes the nitrogen ring system to a considerable extent. This explanation is supported by the fact that tetrahydrothebaine undergoes demethylation rather than ring cleavage.[74] Demethylation rather than ring cleavage of morphine and codeine is one reason for assigning the double bond in these compounds to position 7–8 rather than to position 8–14.

When optically active dibenzoylapomorphine (XVI) is treated with cyanogen bromide in chloroform solution, there is obtained a 50% yield of a product resulting from ring opening and simultaneous loss of hydrogen bromide.[75] Though the analytical figures obtained for the
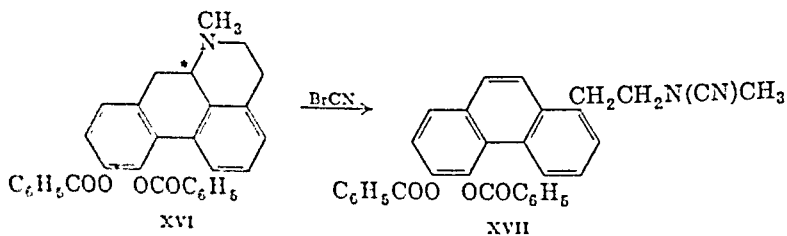
product are equally satisfactory for a compound arising from demethylation without ring opening, structure (XVII) is assigned on the basis of the observed loss in optical activity. Furthermore, the course of the reaction as indicated is consistent with the known lability of a benzyl linkage.

In connection with the problem of the determination of the structure of lupinine, Winterfeld and Holschneider [76] have treated lupinane (XVIII) with cyanogen bromide in boiling benzene. Occurrence of the

[74] von Braun and Aust, Ber., 50, 43 (1917).
[75] Winterfeld and Holschneider, Ber., 64, 137 (1931).

ring cleavage predominantly in the direction indicated, rather than with fission of the other ring, was demonstrated by degradation of the
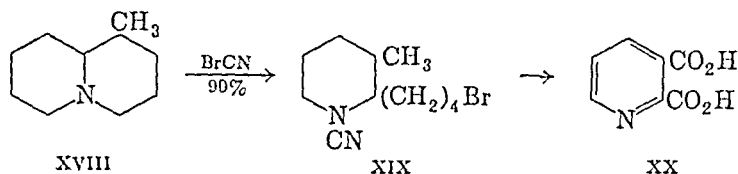
product (XIX) to quinolinic acid (XX). Had ring cleavage in the reverse direction predominated, the ultimate product would have been α-picolinic acid.

Sparteine (XXI) reacts with cyanogen bromide [77] to yield three ring-

opened products, one resulting from the addition of two moles of cyanogen bromide and two incorporating one mole of cyanogen bromide, whose structures have not been determined.
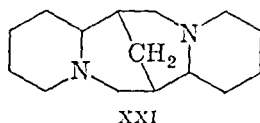
When treated with cyanogen bromide in chloroform solution, cocaine (XXII) undergoes ring opening to only a very slight extent; demethylation is the predominant reaction.[78] Some cocaine methobromide results from reaction of the liberated methyl bromide with cocaine.
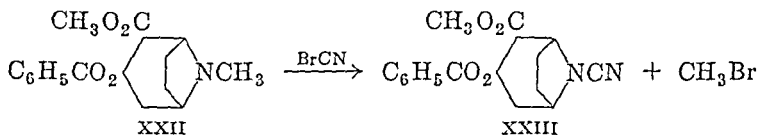
Treatment of the reaction product (XXIII) with concentrated hydrochloric acid at 120° causes the elimination of benzoic acid and removal of the cyano group, thereby yielding desmethylanhydroecgonine. The ethyl ester of anhydroecgonine (XXIV) cannot be demethylated by cyanogen bromide in an appreciable yield because of extensive ring cleavage.[78] The enhanced lability of the ring in XXIV can be attributed to the presence of β,γ unsaturation.
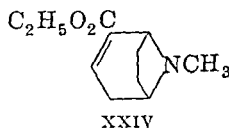
[77] Winterfeld and Holschneider, *Arch. Pharm.*, **267**, 433 (1929).
[78] von Braun and Müller, *Ber.*, **51**, 235 (1918).

SYNTHETIC APPLICATIONS

Occasional mention of the synthetic value of the von Braun cyanogen bromide reaction can be found in the literature.[3, 5, 55, 57, 79, 80] The adoption of this reaction for large-scale synthesis is limited by the properties of cyanogen bromide; its toxicity and volatility discourage the handling of large quantities of cyanogen bromide. The instability of cyanogen bromide makes it inadvisable to attempt to store large quantities of it for an indefinite period. Consequently, use of the cyanogen bromide reaction in synthesis is at present restricted to the field of rare chemicals. The following survey of some applications, together with a few suggested uses, is intended to provide an evaluation of the potentialities of the reaction in syntheses.

The preparation of alkyl bromides by the cleavage of acyclic amines with cyanogen bromide finds only limited use, since these bromides are obtained more readily by other methods. However, the cyanogen bromide reaction does provide a convenient synthesis of bromoaceto-nitrile (p. 228) and of o-vinylbenzyl bromide (p. 228).

The alkylation of cyanamide frequently offers a convenient synthesis of dialkylcyanamides containing two identical substituents, but this method is of little value when two different substituents are desired. The direct introduction of an aryl group into cyanamide is also not readily accomplished. To obtain a cyanamide containing one aryl and one alkyl group, it is often possible to remove one alkyl group from a dialkylarylamine by treatment with cyanogen bromide. Cressman [80] has employed the cyanogen bromide reaction for the preparation of monoalkyl α-naphthylcyanamides from dialkyl α-naphthylamines. The hydrolysis of unsymmetrically substituted cyanamides offers a means of obtaining unsymmetrical secondary amines in a pure state. Since guanidines are readily prepared by the reaction of cyanamides with amine salts,[81] the applicability of the cyanogen bromide reaction to the synthesis of unsymmetrically substituted guanidines is apparent.

$$
\begin{array}{c} R' \\ \diagdown \\ \diagup \\ R \end{array}\!\!NCN + R''NHR'''\cdot HX \rightarrow \begin{array}{c} R' \quad \overset{NH}{\overset{\|}{N}}\ R'' \\ \diagdown\ \diagup\ \diagdown \\ \diagup\ \ \diagup\ \ \diagdown \\ R \qquad\quad R''' \end{array}\!\!\cdot HX
$$
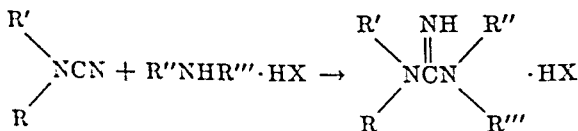
The bromoalkylcyanamides obtained by ring cleavage are more useful since they can be employed in the synthesis of compounds that

[79] von Braun, *Ber.*, **41**, 2113 (1908).

[80] Cressman, *Org. Syntheses*, **27**, 56 (1947).

[81] Erlenmeyer, *Ann.*, **146**, 258 (1868).

frequently are difficult to obtain by other methods. The β-bromoethyl-alkylcyanamides resulting from the ring opening of 1-alkylethylen-imines react with primary amines to yield various cyclic guanidine derivatives and with secondary amines to give, after hydrolysis, unsym-metrical derivatives of ethylenediamine.[5] The products obtained by the

$$BrCH_2CH_2N(CN)R + R'NH_2 \rightarrow \begin{array}{c} CH_2{-\!\!-\!\!-}CH_2 \\ | \qquad\qquad | \\ RN \qquad\qquad NR'\cdot HBr \\ \diagdown\qquad\diagup \\ C \\ \| \\ NH \end{array}$$

$$BrCH_2CH_2N(CN)R + R'NHR'' \rightarrow \begin{array}{c} R'' \\ \diagdown \\ NCH_2CH_2N(CN)R \\ \diagup \\ R' \end{array}$$

$$\downarrow H_2O$$

$$\begin{array}{c} R'' \\ \diagdown \\ NCH_2CH_2NHR \\ \diagup \\ R' \end{array}$$
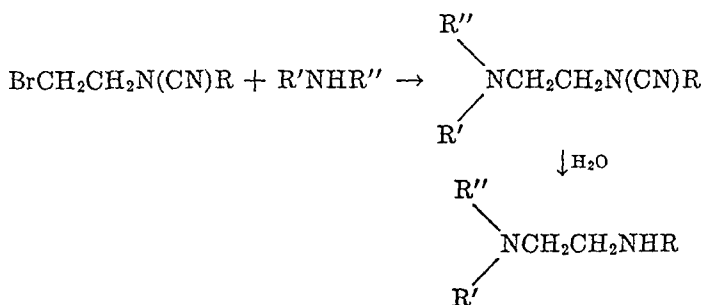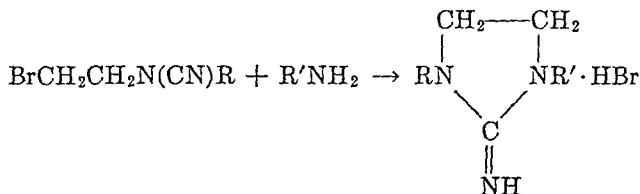
ring opening of 1-alkylpyrrolidines have served as intermediates for the preparation of derivatives of putrescine [5] and monoalkylamino deriva-tives

$$Br(CH_2)_4N(CN)R + R'NHR'' \rightarrow R'R''N(CH_2)_4N(CN)R$$

$$\downarrow H_2O$$

$$R'R''N(CH_2)_4NHR$$
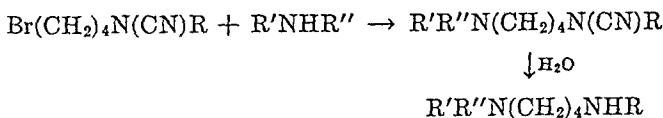
of valeric acid.[47] The product from the cleavage of N-phenylpiperidine

$$RN(CN)(CH_2)_4Br \xrightarrow[\text{(2) Hydrolysis}]{\text{(1) NaCN}} RNH(CH_2)_4COOH$$
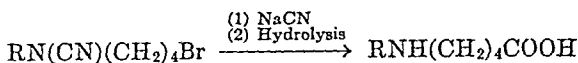
with cyanogen bromide has been used for the synthesis of N,N'-diphenyl-cadaverine.[57]

The above examples illustrate some applications of bromoalkylcyan-amides to the synthesis of compounds through replacement of the bromine atom by nucleophilic reagents without altering the cyanamide portion of the molecule. Though the recorded examples of the use of these bromoalkylcyanamides are few, they suggest a wide variety of applications to be investigated.

EXPERIMENTAL CONDITIONS AND PROCEDURES

Solvents. Many procedures in the literature describe the reaction of amines with cyanogen bromide in the absence of a solvent. This practice frequently gives poor yields because of unfavorable side reactions. Particularly for amines that react vigorously with cyanogen bromide, the use of a diluent is necessary to keep the reaction under control. With the less reactive derivatives of aromatic amines a solvent is less essential and has frequently been omitted.[80] The omission of a solvent appears to offer little or no advantage. If a reaction requires heating, the selection of a solvent having an appropriate boiling point affords a simple means of maintaining adequate temperature control. The physical properties of cyanogen bromide are such (m.p. 52°; b.p. 62°) that heating a reaction mixture containing no solvent occasionally results in a clogged condenser. The use of a solvent accompanied by stirring gives more intimate mixing and avoids excessive local heating.

Non-polar solvents such as ether, chloroform, benzene, and the hydrocarbons are to be preferred because of their immiscibility with water and their tendency to precipitate such by-products as amine salts, which can then be removed by filtration. Dry dioxane is a suitable solvent for the reaction but is to be avoided, if possible, since its miscibility with water complicates working up the reaction mixture. Though glacial acetic acid has been used,[82] hydroxylated solvents are generally less desirable. Reasonably anhydrous conditions are recommended to avoid interference associated with formation of hydrobromic acid.

Order of Mixing Reactants. An important factor is the order of addition of the reactants. As a general rule, the gradual addition of a solution of amine to a solution of cyanogen bromide is preferred. The reasons for this preference become evident when the predominant side reactions are considered. When highly reactive bromides such as allyl, benzyl, and methyl bromide are formed in the reaction, the presence of excess amine is conducive to the formation of quaternary ammonium bromides. Usually cyanogen bromide reacts with an amine more rapidly than do alkyl bromides,[1] and use of the recommended order of addition minimizes this side reaction. Since hydrogen bromide reacts more rapidly with amines than does cyanogen bromide, the order of addition in elimination reactions in which hydrogen bromide is formed is of relatively little importance. Here the yields of olefin and disubstituted cyanamide are limited to a maximum of 50%, regardless of the order of addition.

If an amine is not very reactive toward cyanogen bromide, it will probably not react rapidly with an alkyl bromide. For such amines the simplest procedure is to mix the amine and cyanogen bromide in an appropriate solvent and then heat for the required time. Unless warranted by some special circumstance, such as the desire to cleave an amine in the presence of a thio ether group or to bring about preferential reaction of one of two amine functions present in the same molecule, the gradual addition of cyanogen bromide to an amine should be avoided.

With sensitive amines such as the ethylenimines it is almost imperative that the recommended order of addition be followed, since these amines tend to undergo extensive polymerization initiated by traces of a reactive alkyl halide or an acid.[83]

Isolation of Products. Procedures for the reaction of an amine with cyanogen bromide are generally simple and not subject to wide variation. A greater variety of procedures is involved in working up the reaction mixture and in the isolation of a particular reaction product. The amine and cyanogen bromide are allowed to react either without a solvent or, more frequently, in an inert, water-immiscible solvent such as ether, benzene, or chloroform. After completion of the reaction the addition of more solvent precipitates the major part of any quaternary ammonium salt or amine hydrobromide formed as by-products. Extraction of the solution with dilute aqueous acid removes any unreacted amine and the last traces of salts. The alkyl bromide and the cyanamide remaining in the organic layer can frequently be separated by fractional distillation. If distillation or crystallization does not effect a separation, the choice of another method depends upon whether the alkyl bromide or the cyanamide is the preferred product. By refluxing the mixture with hydrobromic acid it is often possible to hydrolyze the cyanamide to the amine hydrobromide and then isolate the desired alkyl bromide by steam distillation or extraction. If a particular derivative of the alkyl bromide is sought, it is often possible to carry out the reaction involving the alkyl bromide in the presence of the contaminating cyanamide and then to separate the derivative from the cyanamide. More frequently the cyanamide is the desired product. In such cases the contaminating alkyl bromide can be removed readily by reaction with a secondary or tertiary amine, followed by a separation of the amine salts from the neutral cyanamide.

These methods are generally applicable to cyclic as well as to acyclic amines. A paper by von Braun [3] is of particular interest in regard to the

[83] Fruton, in Elderfield, *Heterocyclic Compounds*, Vol. 1, p. 70, John Wiley & Sons, New York, 1950; Lassell and Sundet, *J. Am. Chem. Soc.*, **63**, 2374 (1941).

use of different methods for separating the products resulting from the reaction of several piperidine derivatives with cyanogen bromide.

Preparation and Properties of Cyanogen Bromide. A convenient preparation of cyanogen bromide in 200–300-g. quantities and in 73–85% yield from bromine and sodium cyanide is described in *Organic Syntheses.*[84] In contrast to a note in this procedure on the instability of cyanogen bromide, the author has found that no decomposition occurred after storing in a glass-stoppered flask at room temperature for as long as a month. *The toxicity and volatility of cyanogen bromide require that all operations with this material be performed in an efficient hood.*

The cleavage of dimethyl-α-naphthylamine with cyanogen bromide to furnish methyl-α-naphthylcyanamide in 63–67% yield is described in *Organic Syntheses.*[80]

Bromoacetonitrile.[79] When 200 g.* (1.61 moles) of N-cyanomethylpiperidine is mixed with 171 g. (1.61 moles) of cyanogen bromide, an exothermic reaction occurs, accompanied by the formation of a solid. After the reaction has subsided, the mixture is allowed to stand overnight. Though the reaction is essentially complete at this stage, the mixture is heated for a short time on the steam bath. This heating removes the greater part of any unreacted cyanogen bromide. Ether is added to the cooled reaction mixture, and the solid (quaternary salt formed by reaction of 1-cyanomethylpiperidine with bromoacetonitrile) is removed by filtration. The ether solution is extracted with water to remove the last traces of the quaternary salt, the solvent is removed, and the residual yellow oil is vacuum distilled. There is obtained 135–140 g. (about 70%) of bromoacetonitrile collected over the range 50–90°/15 mm., the greater part distilling at 50°. The residual N-cyanopiperidine distills at 115°/15 mm.

The crude bromoacetonitrile is pure enough for most purposes. A second distillation gives the pure product, a strongly lachrymatory liquid, b.p.46°/13 mm. or 150–151[b]/752 mm.

o-Vinylbenzyl Bromide.[55] Treatment of an ice-cold ether solution of *o*-vinylbenzyldimethylamine with cyanogen bromide causes the precipitation of di-(*o*-vinylbenzyl)dimethylammonium bromide, m.p. 178–179°. After filtration, the ether solution containing the *o*-vinylbenzyl bromide and dimethylcyanamide is extracted with dilute aqueous acid to remove unchanged amine and the water-soluble dimethylcyanamide. After drying the ether solution over calcium chloride and removing the

<hr>

[84] Hartman and Dreger, *Org. Syntheses, Coll. Vol.* II, p. 150, John Wiley & Sons, New York, 1941.

* When small amounts of materials are used, the heat evolved is insufficient to cause an appreciable reaction. The mixture is heated on the steam bath for two to three hours in a sealed tube.

ether, a colorless oil remains. Distillation gives colorless, analytically pure *o*-vinylbenzyl bromide, b.p. 119–120°/17 mm., in 50% yield.

n-Butyl-β-bromoethylcyanamide.[5] A solution of 65 g. (0.65 mole) of 1-*n*-butylethylenimine in 300 ml. of absolute ether is added during four hours with stirring to a solution of 75 g. (0.71 mole) of cyanogen bromide in 200 ml. of ether. The heat of reaction is sufficient to maintain gentle refluxing of the ether. The mixture is allowed to stand overnight, and the clear, pale yellow ether solution is extracted with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water and then dried over calcium chloride. Removal of the ether and distillation of the residue (131 g.) gives 126 g. (94%) of *n*-butyl-β-bromoethylcyanamide as a colorless liquid, b.p. 106–108°/0.6 mm.

n-Butyl-4-bromopentylcyanamide and *n*-Butyl-(1-methyl-4-diethyl-aminobutyl)cyanamide.[5] Addition over a four-hour period of a solution of 70.5 g. (0.50 mole) of 1-*n*-butyl-2-methylpyrrolidine in 200 ml. of benzene to a stirred solution of 58.2 g. (0.55 mole) of cyanogen bromide in 200 ml. of benzene gives a clear, pale yellow solution which is allowed to stand overnight. The benzene solution is extracted with 100 ml. of 5% hydrochloric acid and with two 100-ml. portions of water and dried over calcium chloride. Removal of the benzene under reduced pressure leaves 120 g. of a clear red-brown liquid. The theoretical yield of ring-opened product is 123 g.

This crude product (a mixture of isomers) is refluxed for three and one-half hours with 292 g. (4.0 moles) of diethylamine. After removal of excess diethylamine by distillation, the residue is treated with a solution of 50 ml. of concentrated hydrochloric acid in 200 ml. of water. The acid-insoluble oil is taken up in 350 ml. of ether and dried over calcium chloride. Removal of the ether leaves 32 g. of *n*-butyl-4-bromo-pentylcyanamide as a yellow liquid.

The hydrochloric acid extract is made strongly basic with potassium hydroxide. The oil that separates is taken up in 400 ml. of ether and dried over potassium carbonate. Removal of the ether and traces of diethylamine leaves 81 g. of a clear red-brown liquid. Distillation of 41 g. of this crude basic product gives 36 g. of *n*-butyl-(1-methyl-4-di-ethylamino-butyl)cyanamide as a pale yellow oil, b.p. 130–133°/0.7 mm.

Cyanonorcocaine.[78] Cyanogen bromide (30 g.) is added to a solution of 100 g. of cocaine in 200 ml. of chloroform and the mixture refluxed on the steam bath for two hours. After removal of the chloroform the solid residue is treated with water. From the water solution there is obtained 8 to 9 g. of crude cocaine methobromide. One recrystallization of the water-insoluble solid from ethanol containing a little water gives 62–65 g. (60–63%) of pure cyanonorcocaine, m.p. 123–124°.

RELATIVE EASE OF CLEAVAGE OF AMINES BY CYANOGEN BROMIDE

No accurate tabulation of the relative lability of the various alkyl groups in respect to cleavage from amine nitrogen by cyanogen bromide can be constructed on the basis of the experimental work recorded in the literature.

Table I provides a general picture of the relative lability of the majority of the groups that have been studied. References concerning the groups listed in Table I are not included because an intricate system of cross references would be required. An amine containing a particular alkyl group listed in Table I can be located in Table III where it is accompanied by a literature reference. To emphasize the relation between some general classes of alkyl groups, the table has been arranged in three columns. Column A contains groups of the allyl type, the greater number of which have been compared directly with the unsubstituted allyl group. Column B is similarly arranged on the basis of the benzyl group; Column C with reference to the methyl group. The table is arranged in order of decreasing ease of removal of the group by cyanogen bromide. If two groups are widely separated vertically in the table, one can be reasonably sure that the group higher in the table will be cleaved much more readily than the lower member.

An evaluation of the relative lability of the rings in various cyclic amines can be made with more certainty than the relative lability of the alkyl groups mentioned above. By determining the ratio of ring opening to dealkylation of a particular cyclic amine as the substituents on the nitrogen are varied, a satisfactory estimation of the lability of the ring can be obtained. Though no quantitative conclusions are justified, the ring systems in Table II can be arranged on the basis of their relative lability with reasonable qualitative accuracy. The order of lability given is applicable only to the simple ring systems containing no activating or deactivating substituents in the ring. For example, a phenyl group in the 2 position of tetrahydroquinoline will cause this ring system to be more labile than the pyrrolidine ring. A few of the more pertinent references dealing with the ring systems listed are included.

TABLE I

Relative Ease of Removal of Alkyl Groups

(Descending in Order of Decreasing Lability)
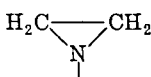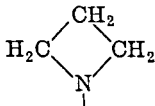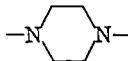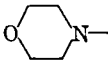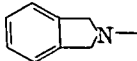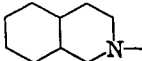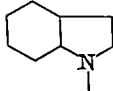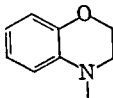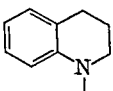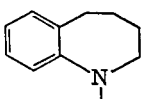
A	B	C
	Methylene (diamines)	
	p-Methoxybenzyl	
	[p-Phenyl, p-cyclohexyl, and p-xenylbenzyl] *	
	p-Ethylbenzyl	
	p-Methylbenzyl	
γ-Phenylallyl		
γ-Ethylallyl		
γ-Methylallyl		
Allyl		
α-Thienyl		
α-Furomethyl		
2-Cyclopentenyl	m-Methyl- and o-phenyl-benzyl	
	[*Benzyl* and o-, m-, p-fluorobenzyl]	
	α-Naphthylmethyl	
[γ-n-Amylpropargyl, propargyl, and cyclopropylmethyl]	β-Naphthylmethyl	
γ-Chloroallyl	p-Chlorobenzyl	
γ-Bromoallyl	p-Bromo- and m-chloro-benzyl	
β-Chloroallyl	p-Iodo- and p-acetamido-benzyl	
β-Bromoallyl	m-Bromo- and m-acetamido-benzyl	
	m-Iodobenzyl	
	o-Chloro- and o-acetamido-benzyl	
	o-Bromobenzyl	
	o-Iodobenzyl	
	p-Cyanobenzyl	
	o- and m-Cyanobenzyl	
	o-, m- and p-Nitrobenzyl	*Methyl*
		[Ethyl, cyanomethyl, and carbalkoxymethyl]
		[Cyclobutylmethyl and n-propyl]
		Phenethyl
		γ-Phenylpropyl
		Isopropyl and n-butyl
		n-Amyl and isoamyl
		[Isobutyl, n-hexyl and higher homologs]

* Groups within brackets are of equivalent lability.

TABLE II

RELATIVE EASE OF RING CLEAVAGE OF CYCLIC AMINES

Amines Descending in Order of Decreasing Ease of Cleavage	References

5

64

62,53,61

51

5,47,48,85

3,7

58,63

Note: References 85–112 are listed on p. 262.

TABULAR SURVEY

Tables III, IV, and V contain most of the known examples of the reaction of tertiary amines with cyanogen bromide involving the reaction discussed in this chapter. Particularly with respect to the alkaloids, the coverage is incomplete since a direct reference to the use of cyanogen bromide is often lacking. The literature has been covered through the year 1950.

Only the major products are listed in the tables. Where yields are available they appear in parentheses next to the product concerned. In several instances in which alkaloids were treated with cyanogen

bromide, either no structures or incorrect structures of the products were reported. Where correct structures are now available, these have been given rather than those reported in the reference cited.

The acyclic amines are covered in Table III, which is divided into the following sections: (A) Miscellaneous Aliphatic Amines; (B) Derivatives of Allylamine; (C) Derivatives of Benzylamine; (D) Derivatives of Other Arylmethylamines; (E) Derivatives of Aromatic Amines. Amines containing both the allyl and the benzyl groups are listed under Derivatives of Allylamine. Aromatic amines that contain the allyl and benzyl groups are listed under Derivatives of Aromatic Amines.

Table IV contains all cyclic amines except the alkaloids. It is divided into the following sections: (A) Three- and Four-Membered Rings (ethylenimines and azetidines); (B) Five-Membered Rings (pyrrolidines, dihydroindoles, and dihydroisoindoles); (C) Six- and Seven-Membered Rings (including piperidines, tetrahydroquinolines, morpholines, and piperazines). Bicyclic amines containing both five- and six-membered rings are included in this section. (D) Pyridine-Type Amines. Most of the examples in section D involve reactions of pyridines, quinolines, and related compounds with cyanogen bromide in which cyanogen bromide is considered to add across the 1,2 double bond to yield a 2-bromo-1-cyano-1,2-dihydro derivative. Occasionally the presence of nuclear substituents causes the cyanogen bromide to add 1,4 (see p. 219).

In Table V are listed most of the alkaloids whose reactions with cyanogen bromide are reported in the literature. Where the course of the reaction and the structure of the products are not known, only the empirical formulas are given.

In Table V and within the various sections of Tables III and IV the amines are listed in order of increasing number of carbon atoms.

TABLE III.

Acyclic Amines

Amine	Products	Reference
A. Miscellaneous Aliphatic Amines		
C_4–C_9		
$(CH_3)_2NCH_2CN$	$CH_3N(CN)CH_2CN + [(CH_3)_3NCH_2CN]Br$ (ca. 50%)	42
$[(CH_3)_2N]_2CH_2$	$(CH_3)_2NCN + CH_2Br_2$	44
$(C_2H_5)_2NCH_2CN$	$C_2H_5N(CN)CH_2CN$ (40%) $+ BrCH_2CN$ (50%)	42
$(n\text{-}C_3H_7)_2NCH_3$	$(n\text{-}C_3H_7)_2NCN + CH_3Br$	1
$CH_2{=}CH(CH_2)_3N(CH_3)_2$	$CH_2{=}CH(CH_2)_3N(CN)CH_3 + [CH_2{=}CH(CH_2)_3N(CH_3)_3]Br$	35
$(n\text{-}C_3H_7)_2NC_2H_5$	$(n\text{-}C_3H_7)_2NCN + C_2H_5Br$	1
$(n\text{-}C_3H_7)_2NCH_2CN$ *	$(n\text{-}C_3H_7)_2NCN + n\text{-}C_3H_7N(CN)CH_2CN$ (20–25%)	42
$(C_2H_5)_2NCH_2CO_2C_2H_5$	$(C_2H_5)_2NCN$ † $+ C_2H_5N(CN)CH_2CO_2C_2H_5$	42
$(n\text{-}C_3H_7)_3N$	$(n\text{-}C_3H_7)_2NCN + n\text{-}C_3H_7Br + (n\text{-}C_3H_7)_3N \cdot HBr$	1
C_{10}–C_{15}		
$[(CH_3)_2CHCH(CH_2)]_2NCH_2CN$	$[(CH_3)_2CHCH(CH_2)]_2NCN + BrCH_2CN$	42
$(n\text{-}C_3H_7)_2NCH_2CO_2C_2H_5$	$n\text{-}C_3H_7N(CN)CH_2CO_2C_2H_5 + (n\text{-}C_3H_7)_2NCN$	42
$C_6H_5(CH_2)_2N(CH_3)_2$	$C_6H_5(CH_2)_2N(CN)CH_3 + [C_6H_5(CH_2)_2N(CH_3)_3]Br$ (40%)	37
$C_6H_5(CH_2)_3N(CH_3)_2$	$C_6H_5(CH_2)_3N(CN)CH_3 + [C_6H_5(CH_2)_3N(CH_3)_3]Br$ (33%)	37
$[(CH_3)_2CHCH CH_2]_2NCH(CH_3)_2$	No products isolated	42
$C_6H_5(CH_2)_2N(C_2H_5)_2$	$C_6H_5(CH_2)_2N(CN)C_2H_5$ (70%) $+ C_2H_5Br$	37
$C_6H_5(CH_2)_3N(C_2H_5)_2$	$C_6H_5(CH_2)_3N(CN)C_2H_5$ (75%) $+ (C_2H_5)_2NCN$ (25%) $+ C_6H_5(CH_2)_3Br$	37
$[(CH_3)_2CHCH_2CH_2CH_2NCH(CH_3)_2]_2$	No products isolated	42
$[(n\text{-}C_3H_7)_2N]_2CH_2$	$(n\text{-}C_3H_7)_2NCN + CH_2Br_2$	44
$C_6H_5(CH_2)_3N(C_3H_{7}\text{-}n)_2$	$C_6H_5(CH_2)_3N(CN)C_3H_{7}\text{-}n$ (65%) $+ n\text{-}C_3H_7Br + (n\text{-}C_3H_7)_2NCN$ (35%) $+ C_6H_5(CH_2)_3Br$ (35%)	37
B. Derivatives of Allylamine		
C_7–C_9		
$(CH_2{=}CClCH_2)_2NCH_3$	$CH_2{=}CClCH_2N(CN)CH_3 + CH_2{=}CClCH_2Br + [(CH_2{=}CClCH_2)_3NCH_3]Br$	39

Reactant	Product(s)	Reference
$ClCH=CHCH_2N(CH_3)CH_2CH=CHBr$	Mixed cyanamides + mixed bromides	39
$CH_2=CClCH_2N(CH_3)CH_2CH=CHBr$	$CH_2=CClCH_2N(CN)CH_3 + BrCH=CHCH_2Br$	39
$CH_2=CBrCH_2N(CH_3)CH_2CH=CHBr$	$CH_2=CBrCH_2N(CN)CH_3 + BrCH=CHCH_2Br$	39
$CH_2=CClCH_2N(CH_3)CH_2CBr=CH_2$	Mixed cyanamides + mixed bromides	39
$(CH_2=CBrCH_2)_2NCH_3$	$CH_2=CBrCH_2N(CN)CH_3 + CH_2=CBrCH_2Br$	39
$(ClCH=CHCH_2)_2NCH_3$	$ClCH=CHCH_2N(CN)CH_3 + ClCH=CHCH_2Br$	39
$CH_2=CHCH_2N[CH(CH_3)_2]_2$	$[(CH_3)_2CH]_2NCN + CH_2=CHCH_2Br$	4
$CH=CH$ $\rangle CHN(C_2H_5)_2$ CH_2-CH_2 $\quad C_{11}-C_{17}$	$(C_2H_5)_2NCN +$ amine hydrobromide ‡	34
$C_6H_5CH=CHCH_2N(CH_3)_2$	$(CH_3)_2NCN + C_6H_5CH=CHCH_2Br$	35
$ClCH=CHCH_2N(CH_3)CH_2C_6H_5$	$ClCH=CHCH_2N(CN)CH_3 + C_6H_5CH_2Br$	39
$CH_2=CBrCH_2N(CH_3)CH_2C_6H_5$	$CH_2=CBrCH_2N(CN)CH_3 + C_6H_5CH_2Br$	39
$\left[\begin{smallmatrix}CH=CH\\ CH_2-CH_2\end{smallmatrix}\rangle CH\right]_2NCH_3$	$CH=CH$ $\rangle CHN(CN)CH_3 +$ amine hydrobromide ‡ CH_2-CH_2	34
$CH=CH$ $\rangle CHN(CH_3)CH_2C_6H_5$ CH_2-CH_2 $\quad C_{18}-C_{23}$	Inseparable mixture of two cyanamides + amine hydrobromide ‡	34
$p\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2CH=CHCH_3$	$CH_3CH=CHCH_2N(CN)CH_3 + p\text{-}CH_3C_6H_4CH_2Br$	16
$C_6H_5CH=CHCH_2N(CH_3)CH_2CH=CH_2$	$CH_2=CHCH_2N(CN)CH_3 + C_6H_5CH=CHCH_2Br$	16
$C_6H_5CH=CHCH_2N(CH_3)CH_2CH=CHCH_3$	$CH_3CH=CHCH_2N(CN)CH_3 + C_6H_5CH=CHCH_2Br$	16
$(C_6H_5CH_2)_2NCH_2CH=CH_2$	$(C_6H_5CH_2)_2NCN + CH_2=CHCH_2Br$	36
$p\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2CH=CHC_6H_5$	$C_6H_5CH=CHCH_2N(CN)CH_3 + p\text{-}CH_3C_6H_4CH_2Br$	16
$p\text{-}C_6H_5C_6H_4CH_2N(CH_3)CH_2CH=CHC_6H_5$	$C_6H_5CH=CHCH_2N(CN)CH_3 + p\text{-}C_6H_5C_6H_4CH_2Br$	16

* This reaction was carried out in a sealed tube at 100°

† The cyanamides were obtained in nearly equivalent amounts. Bromides were not isolated.

‡ No cyclopentenyl bromide was isolated.

TABLE III—Continued

ACYCLIC AMINES

Amine	Products	Reference
C₉–C₁₃		
o-ClC₆H₄CH₂N(CH₃)₂	(CH₃)₂NCN + o-ClC₆H₄CH₂Br + [(o-ClC₆H₄CH₂)₂N(CH₃)₂]Br	39
		39
	(CH₃)₂NCN + p-IC₆H₄CH₂Br	36
p-IC₆H₄CH₂N(CH₃)₂	(C₂H₅)₂NCN + C₆H₅CH₂Br ‖	38
C₆H₅CH₂N(C₂H₅)₂	HC≡CCH₂N(CN)CH₃ + C₆H₅CH₂Br	55
C₆H₅CH₂N(CH₃)CH₂C≡CH	(CH₃)₂NCN + o-CH₂=CHC₆H₄CH₂Br (50%)	38
o-CH₂=CHC₆H₄CH₂N(CH₃)₂		

$$C_6H_5CH_2N(CH_3)CH_2CH\underset{\diagdown CH_2 \diagup}{} \quad\quad CH_2\underset{\diagdown CHCH_2N(CN)CH_3 \diagup}{} + C_6H_5CH_2Br \qquad 36$$

Amine	Products	Reference
C₆H₅CH₂N(C₃H₇-n)₂	(n-C₃H₇)₂NCN + C₆H₅CH₂Br	
C₁₆		
p-FC₆H₄CH₂N(CH₃)CH₂C₆H₅	Mixed cyanamides + mixed bromides	24
p-FC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-p	p-ClC₆H₄CH₂N(CN)CH₃ + p-FC₆H₄CH₂Br	24
o-FC₆H₄CH₂N(CH₃)CH₂C₆H₅	Mixed cyanamides + mixed bromides	24
p-FC₆H₄CH₂N(CH₃)CH₂C₆H₄F-o	Mixed cyanamides + mixed bromides	24
p-BrC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-m	m-ClC₆H₄CH₂N(CN)CH₃ + p-BrC₆H₄CH₂Br	31
m-BrC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-m	m-BrC₆H₄CH₂N(CN)CH₃ + m-ClC₆H₄CH₂Br	31
o-BrC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-o	o-BrC₆H₄CH₂N(CN)CH₃ + o-ClC₆H₄CH₂Br	31
p-BrC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-p	p-BrC₆H₄CH₂N(CN)CH₃ + p-ClC₆H₄CH₂Br	39
m-BrC₆H₄CH₂N(CH₃)CH₂C₆H₄Br-o	o-BrC₆H₄CH₂N(CN)CH₃ + m-BrC₆H₄CH₂Br	31
p-IC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-m	m-ClC₆H₄CH₂N(CN)CH₃ + p-IC₆H₄CH₂Br	31
m-IC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-o	o-ClC₆H₄CH₂N(CN)CH₃ + m-IC₆H₄CH₂Br	31
m-IC₆H₄CH₂N(CH₃)CH₂C₆H₄Br-m	m-BrC₆H₄CH₂N(CN)CH₃ + m-IC₆H₄CH₂Br	31

C. Derivatives of Benzylamine §

o-IC₆H₄CH₂N(CH₃)CH₂C₆H₄Br-o	o-IC₆H₄CH₂N(CN)CH₃ + o-BrC₆H₄CH₂Br	31
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₅	p-O₂NC₆H₄CH₂N(CN)CH₃ + C₆H₅CH₂Br	40
o-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-o	o-O₂NC₆H₄CH₂N(CN)CH₃ + o-ClC₆H₄CH₂Br	40
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-p	p-O₂NC₆H₄CH₂N(CN)CH₃ + p-ClC₆H₄CH₂Br	40
m-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-o	m-O₂NC₆H₄CH₂N(CN)CH₃ + p-ClC₆H₄CH₂Br	40
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-o	p-O₂NC₆H₄CH₂N(CN)CH₃ + o-ClC₆H₄CH₂Br	40
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-m	p-O₂NC₆H₄CH₂N(CN)CH₃ + m-ClC₆H₄CH₂Br	40
o-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄I-o	o-O₂NC₆H₄CH₂N(CN)CH₃ + o-IC₆H₄CH₂Br	40
o-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-m	Mixed cyanamides + mixed bromides	40
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-m	Mixed cyanamides + mixed bromides	40

C₁₆

p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄CN-p	p-O₂NC₆H₄CH₂N(CN)CH₃ + p-NCC₆H₄CH₂Br	40
o-IC₆H₄CH₂N(CH₃)CH₂C₆H₄CN-p	p-NCC₆H₄CH₂N(CN)CH₃ + o-IC₆H₄CH₂Br	40
p-NCC₆H₄CH₂N(CH₃)CH₂C₆H₅	p-NCC₆H₄CH₂N(CN)CH₃ + C₆H₅CH₂Br + [(C₆H₅CH₂)₂N(CH₂)CH₂C₆H₄CN-p]Br	40
p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄F-p	p-FC₆H₄CH₂N(CN)CH₃ + p-CH₃C₆H₄CH₂Br	21
p-CH₃OC₆H₄CH₂N(CH₃)CH₂C₆H₅	C₆H₅CH₂N(CN)CH₃ + p-CH₃OC₆H₄CH₂Br	23
o-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-p	p-ClC₆H₄CH₂N(CN)CH₃ + o-CH₃C₆H₄CH₂Br	31
p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₆	C₆H₅CH₂N(CN)CH₃ + p-CH₃C₆H₄CH₂Br	16
o-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₆	o-CH₃C₆H₄CH₂N(CN)CH₃ + C₆H₅CH₂Br	23
m-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₅	C₆H₅CH₂N(CN)CH₃ + m-CH₃C₆H₄CH₂Br	23

C₁₇

p-CH₃C₆H₄CH₂N(C₂H₅)CH₂C₆H₅	C₆H₅CH₂N(CN)C₂H₅ + p-CH₃C₆H₄CH₂Br	23
o-C₂H₅C₆H₄CH₂N(CH₃)CH₂C₆H₅	Mixed cyanamides + mixed bromides	31
p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄CH₃-m	m-CH₃C₆H₄CH₂N(CN)CH₃ + p-CH₃C₆H₄CH₂Br	23

§ See also Section D, p. 239.
‖ The products are not separable by distillation.

TABLE III—*Continued*

ACYCLIC AMINES

C. Derivatives of Benzylamine—Continued

Amine	Products	Reference
C_{17} (Cont'd)		
$o\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2C_6H_4CH_3\text{-}p$	$o\text{-}CH_3C_6H_4CH_2N(CN)CH_3 + p\text{-}CH_3C_6H_4CH_2Br$	23
$o\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2C_6H_4CH_3\text{-}m$	$o\text{-}CH_3C_6H_4CH_2N(CN)CH_3 + m\text{-}CH_3C_6H_4CH_2Br$	23
$p\text{-}CH_3OC_6H_4CH_2N(CH_3)CH_2C_6H_4CH_3\text{-}p$	$p\text{-}CH_3C_6H_4CH_2N(CN)CH_3 + p\text{-}CH_3OC_6H_4CH_2Br$ $+ [(p\text{-}CH_3OC_6H_4CH_2)_2N(CH_3)CH_2C_6H_4CH_3\text{-}p]Br$	23
$p\text{-}CH_3C_6H_4CH_2N(C_2H_5)CH_2C_6H_4F\text{-}p$	$p\text{-}FC_6H_4CH_2N(CN)C_2H_5 + p\text{-}CH_3C_6H_4CH_2Br$	24
$p\text{-}CH_3CONHC_6H_4CH_2N(CH_3)CH_2C_6H_4Cl\text{-}p$	$p\text{-}CH_3CONHC_6H_4CH_2N(CN)CH_3 + p\text{-}ClC_6H_4CH_2Br$ $+ [(p\text{-}ClC_6H_4CH_2)_2N(CH_3)CH_2C_6H_4NHCOCH_3\text{-}p]Br$	40
$p\text{-}CH_3CONHC_6H_4CH_2N(CH_3)CH_2C_6H_5$	$p\text{-}CH_3CONHC_6H_4CH_2N(CN)CH_3 + C_6H_5CH_2Br$ $+ [(C_6H_5CH_2)_2N(CH_3)CH_2C_6H_4NHCOCH_3\text{-}p]Br$	40
$p\text{-}CH_3CONHC_6H_4CH_2N(CH_3)CH_2C_6H_4I\text{-}o$	$p\text{-}CH_3CONHC_6H_4CH_2N(CN)CH_3 + o\text{-}IC_6H_4CH_2Br$	40
$p\text{-}NCC_6H_4CH_2N(CH_3)CH_2C_6H_4CN\text{-}m$	$m\text{-}NCC_6H_4CH_2N(CN)CH_3 + p\text{-}NCC_6H_4CH_2Br$	40
$m\text{-}NCC_6H_4CH_2N(CH_3)CH_2C_6H_4CN\text{-}o$	Mixed cyanamide + mixed bromide	40
$C_{18}\text{--}C_{21}$		
$p\text{-}C_2H_5C_6H_4CH_2N(CH_3)CH_2C_6H_4CH_3\text{-}p$	$p\text{-}CH_3C_6H_4CH_2N(CN)CH_3 + p\text{-}C_2H_5C_6H_4CH_2Br$	16
$p\text{-}CH_3OC_6H_4CH_2N(CH_3)CH_2C_6H_4OC_2H_5\text{-}p$	Mixed cyanamides + mixed bromides	31
$o\text{-}C_2H_5C_6H_4CH_2N(CH_3)CH_2C_6H_4CH=CH_2\text{-}o$	Mixed cyanamides + mixed bromides	31
$p\text{-}CH_3CONHC_6H_4CH_2N(CH_3)CH_2C_6H_4NHCOCH_3\text{-}o$	$o\text{-}CH_3CONHC_6H_4CH_2N(CN)CH_3$	40
$o\text{-}CH_3CONHC_6H_4CH_2N(CH_3)CH_2C_6H_4NHCOCH_3\text{-}m$	$o\text{-}CH_3CONHC_6H_4CH_2N(CN)CH_3$	40
$(C_6H_5CH_2)_3N$	$(C_6H_5CH_2)_2NCN + C_6H_5CH_2Br$	1
$p\text{-}C_6H_5C_6H_4CH_2N(CH_3)CH_2C_6H_5$	$C_6H_5CH_2N(CN)CH_3 + p\text{-}C_6H_5C_6H_4CH_2Br$	16
$o\text{-}C_6H_5C_6H_4CH_2N(CH_3)CH_2C_6H_5$	$o\text{-}C_6H_5C_6H_4CH_2Br$ ¶ + unidentified mixture of cyanamides	31
$C_{22}\text{--}C_{23}$		
$p\text{-}CH_3OC_6H_4CH_2N(CH_3)CH_2C_6H_4C_6H_5\text{-}p$	$p\text{-}C_6H_5C_6H_4CH_2N(CN)CH_3 + p\text{-}CH_3OC_6H_4CH_2Br$	23
$p\text{-}CH_3C_6H_4CH_2N(CH_3)CH_2C_6H_4C_6H_5\text{-}p$	$p\text{-}CH_3C_6H_4CH_2N(CN)CH_3 + p\text{-}C_6H_5C_6H_4CH_2Br$	16
$p\text{-}C_2H_5C_6H_4CH_2N(CH_3)CH_2C_6H_4C_6H_5\text{-}p$	$p\text{-}C_2H_5C_6H_4CH_2N(CN)CH_3 + p\text{-}C_6H_5C_6H_4CH_2Br$	16

Mixed cyanamides + mixed bromides

$$CH_2-CH_2$$
$$CH \cdot CH \cdot CH_2N(CH_3)CH_2C_6H_4C_6H_5\text{-}p$$
$$CH_2-CH_2$$
$$CH_2$$
31

$[(C_6H_5CH_2)_2N]_2CH_2$

$p\text{-}(p\text{-Xenyl})C_6H_4CH_2N(CH_3)CH_2C_6H_4C_6H_5\text{-}p$

$(C_6H_5CH_2)_2NCN$

$p\text{-}(p\text{-Xenyl})C_6H_4CH_2Br$ (major) $+ p\text{-}C_6H_5C_6H_4CH_2Br$ (minor)

44
31

D. Derivatives of Other Arylmethylamines

$C_8\text{–}C_{13}$

(furyl)$CH_2N(CH_3)C_2H_5$

$C_2H_5N(CN)CH_3 +$ (furyl)CH_2Br

35

(thienyl)$CH_2N(CH_3)CH_2$ (furyl)

$\left[\text{(furyl)}CH_2 \right]_2 N(CH_3)CH_2C_6H_5 +$ (thienyl)CH_2Br †† $+$ (furyl)CH_2Br

38

(furyl)$CH_2N(CH_3)CH_2C_6H_5$**

$\left[\text{(thienyl)}CH_2 \right]_2 N(CH_3)CH_2C_6H_5 \right] Br +$ (furyl)CH_2Br

38

(thienyl)$CH_2N(CH_3)CH_2C_6H_5$**

$C_6H_5CH_2N(CN)CH_3 +$ (thienyl)CH_2Br

38

(naphthyl)$CH_2N(CH_3)_2$

$(CH_3)_2NCN +$ (naphthyl)CH_2Br

86

Note: References 85–112 are listed on p. 262.
¶ This bromide was identified as its reaction product with trimethylamine.
** Though derivatives of benzylamine, these amines are listed in this section to emphasize the behavior of the α-furfuryl and α-thienyl groups.
†† The products were poorly characterized.

TABLE III—Continued

ACYCLIC AMINES

Amine	Products	Reference

D. Derivatives of Other Arylmethylamines—Continued

C_{13}–C_{23}

CH₂N(CH₃)₂ (naphthalene) → (CH₃)₂NCN + CH₂Br (naphthalene) — 86

CH₂N(CH₃)CH₂C₆H₅ (naphthalene) → CH₂N(CN)CH₃ (naphthalene) + C₆H₅CH₂Br — 86

CH₂N(CH₃)CH₂ (naphthalene) → CH₂N(CN)CH₃ + CH₂Br (naphthalene) — 86

E. Derivatives of Aromatic Amines

C_6–C_{10}

$C_6H_5N(CH_3)_2$	$C_6H_5N(CN)CH_3 + [C_6H_5N(CH_3)_3]Br$	1, 2
$m\text{-}ClC_6H_4N(CH_3)_2$	$m\text{-}ClC_6H_4N(CN)CH_3 + [m\text{-}ClC_6H_4N(CH_3)_3]Br$	45
$m\text{-}CH_3C_6H_4N(CH_3)_2$	$m\text{-}CH_3C_6H_4N(CN)CH_3 + [m\text{-}CH_3C_6H_4N(CH_3)_3]Br$	45
$p\text{-}CH_3C_6H_4N(CH_3)_2$	$p\text{-}CH_3C_6H_4N(CN)CH_3 + [p\text{-}CH_3C_6H_4N(CH_3)_3]Br$ (ca. 75%)	41
$C_6H_5N(CH_3)C_2H_5$	$C_6H_5N(CN)C_2H_5$	1
$p\text{-}BrC_6H_4N(CH_3)CH_2CN$	No reaction	43
$C_6H_5N(CH_3)CH_2CN$ ‡	$p\text{-}BrC_6H_4N(CH_3)CH_2CN$	43
$C_6H_5N(C_2H_5)_2$	$C_6H_5N(CN)C_6H_5$	1, 2
$C_6H_5N(CH_3)C_3H_7\text{-}n$	$C_6H_5N(CN)C_3H_7\text{-}n$	1
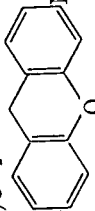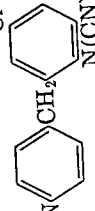
Reactant	Product	Ref.
$C_6H_5N(CH_3)C_3H_7\text{-}i$	$C_6H_5N(CN)C_3H_7\text{-}i$	4
$C_6H_5N(CH_3)CH_2CH=CH_2$	$C_6H_5N(CN)CH_3 + CH_2=CHCH_2Br$	4
$C_6H_5N(CH_3)CH_2C\equiv CH$	$C_6H_5N(CN)CH_3 + HC\equiv CCH_2Br$	38
$C_6H_5N(C_2H_5)CH_2CN$ ††	No reaction	43
$p\text{-}CH_3C_6H_4N(CH_3)CH_2CN$	No definite products isolated	43
$C_6H_5N(CH_3)CH(CH_3)CN$		43

C_{11}-C_{13}

Reactant	Product	Ref.
$C_6H_5N(CH_3)CH_2CH$—CH_2 (cyclopropane, CH_2 bridge)	CH—$CHCH_2Br$ (cyclopropane, CH_2 bridge) ; $C_6H_6N(CN)CH_3 + CH_2$—$CHCH_2CH_3$ (cyclopropane) (37%)	38
$p\text{-}(i\text{-}C_3H_7)C_6H_4N(CH_3)_2$	$p\text{-}(i\text{-}C_3H_7)C_6H_4N(CN)CH_3$	87
$C_6H_5N(C_2H_5)C_3H_7\text{-}n$	$C_6H_5N(CN)C_3H_7\text{-}n$	1
$C_6H_5N(C_2H_5)C_3H_7\text{-}i$	$C_6H_5N(CN)C_3H_7\text{-}i$	4
$C_6H_5N(C_2H_5)CH_2CH=CH_2$	$C_6H_5N(CN)C_2H_5 + CH_2=CHCH_2Br$	4
$C_6H_5N(C_3H_7\text{-}n)_2$	$C_6H_5N(CN)C_3H_7\text{-}n + n\text{-}C_3H_7Br$	1
$C_6H_5N(C_3H_7\text{-}n)C_3H_7\text{-}i$	$C_6H_5N(CN)C_3H_7\text{-}i + n\text{-}C_3H_7Br$	4
$C_6H_5N(C_3H_7\text{-}i)_2$	$C_6H_5N(CN)C_3H_7\text{-}i$ + amine hydrobromide	4

Reactant	Product	Ref.
CH_2—CH_2 / CH_2—CH_2 (ring) ; $C_6H_5N(CH_3)CH_2CH_2CH=CH_2$	CH_2—CH_2 / CH_2—CH_2 (ring) ; $C_6H_5N(CN)CH_2CH_2CH$—CH_2	38
$C_6H_5N(C_3H_7\text{-}i)CH_2CH=CH_2$	$C_6H_5N(CN)C_3H_7\text{-}i + CH_2=CHCH_2Br$	4

Reactant	Product	Ref.
$N(CH_3)_2$ (naphthalene)	$N(CN)CH_3$ (naphthalene) §§ (63–67%)	80
$(C_6H_5)_2NCH_3$	No products isolated	1

Note: References 85–112 are listed on p. 262.
†† This reaction was carried out at 100°. No reaction occurs at room temperature.
§§ The ethyl analog was obtained in 48% yield.

TABLE III—*Continued*

ACYCLIC AMINES

E. *Derivatives of Aromatic Amines—Continued*

Amine	Products	Reference
C_{14}–C_{16}		
$C_6H_5N(C_4H_9\text{-}n)C_4H_9\text{-}i$	$C_6H_5N(CN)C_4H_9\text{-}i + n\text{-}C_4H_9Br$	33
(thiophene)–$CH_2N(C_6H_5)CH_2CH=CH_2$	(thiophene)–$CH_2N(CN)C_6H_5 + CH_2=CHCH_2Br$	38
$C_6H_5N(CH_3)CH_2C_6H_5$	$C_6H_5N(CN)CH_3 + C_6H_5CH_2Br$	36
$C_6H_5(CH_2)_2N(CH_3)C_6H_5$	$C_6H_5(CH_2)_2N(CN)C_6H_5$	37
$o\text{-}CH_3C_6H_4CH_2N(CH_3)C_6H_5$	$C_6H_5N(CN)CH_3 + o\text{-}CH_3C_6H_4CH_2Br$ ‖‖	53
$n\text{-}C_4H_9N(C_6H_5)CH_2CH$—$\underset{\underset{CH_2\text{—}CH_2}{\big|}}{CH_2}$	$C_6H_5N(CN)C_4H_9\text{-}n + CH_2$—$\underset{\underset{CH_2\text{—}CH_2}{\big|}}{CHCH_2Br}$	38
$n\text{-}C_5H_{11}N(C_6H_5)C_5H_{11}\text{-}i$	Equal amounts of both cyanamides and bromides	33
$n\text{-}C_3H_7N(C_6H_5)C_5H_{11}\text{-}i$	$C_6H_5N(CN)C_3H_7\text{-}i + C_6H_5CH_2Br$	36
$i\text{-}C_3H_7N(C_6H_5)CH_2C_6H_5$	$C_6H_5N(CN)CH_2C_6H_5 + CH_2=CHCH_2Br$	36
$C_6H_5CH_2N(C_6H_5)CH_2CH=CH_2$		
C_{17}–C_{19}		
$[p\text{-}(CH_3)_2NC_6H_4]CH_2CH_2$	$[p\text{-}CH_3(CN)NC_6H_4]_2CH_2$ (ca. 50%)	45, 88
$HC≡CCH(C_6H_5)CH_2C≡CC_5H_{11}\text{-}n$	$C_6H_5N(CN)CH_2C≡CH$ (60%) $+ n\text{-}C_5H_{11}C≡CCH_2Br$ ¶¶	89
		90
(xanthene: $(CH_3)_2N$ … $N(CH_3)_2$)	(xanthene: $CH_3(CN)N$ … $N(CN)CH_3$) (45%)	45
(Cl-substituted diarylmethane: $(CH_3)_2N$ … $N(CH_3)_2$)	(Cl-substituted diarylmethane: $CH_3(CN)N$ … $N(CN)CH_3$)	

Reactant	Product	Refs.
$(CH_3)_2N$— —CH_2— —CH_3 / $N(CH_3)_2$	CH_3 / CH_2— —$N(CN)CH_3$ / $CH_3(CN)N$—	45
$(CH_3)_2N$— —$N(CH_3)_2$ / CH_3	No reaction	46
$(CH_3)_2N$— —$N(CH_3)_2$ / CH_3	$CH_3(CN)N$— —$N(CN)CH_3$ (ca. 40%) / CH_3	46
$(CH_3)_2N$— —CH_2— —$N(CH_3)_2$ / CH_3	$CH_3(CN)N$— —$N(CN)CH_3$ / CH_3 / CH_2	45
$(C_6H_5)_3N$ / $[C_6H_5N(CH_3)]_2(CH_2)_5$	No products isolated $[C_6H_5N(CN)]_2(CH_2)_5$	1, 57
$(CH_3)_2N$— —CH_2— —$N(CH_3)_2$ / CH_3	No reaction	45
$(CH_3)_2N$— —CH_2— —$N(CH_3)_2$ / CH_3	No reaction	45
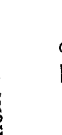
Note: References 85–112 are listed on p. 262.

‖ The products were poorly characterized.

¶¶ Appreciable cleavage in the other direction was observed.

TABLE III—*Continued*

ACYCLIC AMINES
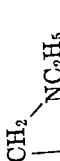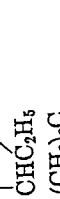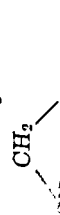
Amine	Products	Reference

E. Derivatives of Aromatic Amines—Continued

C_{12} (*Cont'd*)

H₃C—C₆H₃(CH₃)—CH₂—C₆H₄—N(CH₃)₂	No reaction	45
(CH₃)₂N—C₆H₄—CH₂— with CH₃	No reaction	45
(CH₃)₂N—C₆H₄—CH₂—C₆H₃(CH₃)—N(CH₃)₂	CH₃(CN)N—C₆H₃(CH₃)—CH₂—C₆H₃(CH₃)—N(CN)CH₃	45

C_{20}–C_{24}

(CH₃)₂N—C₆H₄—P(C₆H₅)₂ *	An oil which on treatment with water yielded $(CH_3)_2N-C_6H_4-\overset{O}{P}(C_6H_5)_2 \cdot H_2O$	25
[p-(CH₃)₂NC₆H₄]₂CHCC₆H₅	$C_6H_5CH[C_6H_4N(CN)CH_3\text{-}p]_2$ (ca. 75%)	91
C₆H₅CH=CHCH₂N(C₆H₅)CH₂C≡CC₆H₅	$C_6H_5C \equiv CCH_2N(CN)C_6H_5(?)$	89

Note: References 85–112 are listed on p. 262.
* No reaction took place at the amino group.

TABLE IV

CYCLIC AMINES

A. *Three- and Four-Membered Rings*
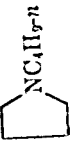
Amine	Products	Reference
C_4–C_7		
(CH₂–NC₂H₅ / CH₂ aziridine)	$C_2H_5N(CN)CH_2CH_2Br$ (88%)	5
(CH₂–NC₄H₉-n / CH₂ aziridine)	n-$C_4H_9N(CN)CH_2CH_2Br$ (94%)	5
(CH₂–NC₄H₉-n / CHC₂H₅ ring)	n-$C_4H_9N(CN)CH_2CHBrC_2H_5$ (82%) + $CH_3CH=CHCH_2N(CN)C_4H_9$-n (11%) + $C_2H_5CH(NHC_4H_9$-$n)CH_2Br \cdot HBr$ (6%)	5
((CH₃)₂C–NC₄H₉-n / CH₂ ring)	$CH_2=C(CH_3)CH_2N(CN)C_4H_9$-$n$ (29%) + $(CH_3)_2CBrCH_2CH_2NHC_4H_9$-$n \cdot HBr$ * (16%)	5
(CH₂–NC₄H₉-n / CH₂ CH₂ four-membered)	n-$C_4H_9N(CN)CH_2CH_2CH_2Br$ (85%)	5

Note: References 85–112 are listed on p. 262.

* Considerable polymerization of the starting material was observed.

TABLE IV—*Continued*

CYCLIC AMINES

Amine	Products	Reference
	B. Five-Membered Rings	
C_6-C_9		
 NC$_2$H$_5$	$C_2H_5N(CN)(CH_2)_4Br$ † (94%)	48
 NC$_3$H$_7$-n	n-$C_3H_7N(CN)(CH_2)_4Br$ (93%)	48
 NC$_4$H$_9$-n CH$_3$	n-$C_4H_9N(CN)(CH_2)_4Br$ (quant.)	5, 47
 NCH(CH$_3$)$_2$	$(CH_3)_2CHN(CN)CH(CH_3)(CH_2)_3Br$ (61%) + $(CH_3)_2CHN(CN)(CH_2)_3CHBrCH_3$ (30%)	5
 NC$_5$H$_{11}$-n	n-$C_5H_{11}N(CN)(CH_2)_4Br$ (ca. 80%)	85
 NC$_5$H$_{11}$-i CH$_3$	i-$C_5H_{11}N(CN)(CH_2)_4Br$	85
 NC$_4$H$_9$-n	n-$C_4H_9N(CN)CH(CH_2)_3Br$ (70%) + n-$C_4H_9N(CN)(CH_2)_3CHBrCH_3$ $\quad\quad$ CH$_3$ (26%)	5

C$_9$–C$_{11}$	51
NCH$_3$	53
NC$_2$H$_5$	53
	5
	5
	50

CH$_2$CH$_2$Br, N(CN)CH$_3$ (40%)

CH$_2$Br ‡, CH$_2$N(CN)CH$_3$

CH$_2$Br ‡, CH$_2$N(CN)C$_2$H$_5$

n-C$_4$H$_9$-N(CN)CH(CH$_3$)CH$_2$CH$_2$CHBrCH$_3$

CH$_2$=C(CH$_2$)$_3$N(CN)C$_4$H$_9$-n (41%) + amine hydrobromide (42%)
CH$_3$

p-ClC$_6$H$_4$N(CN)(CH$_2$)$_3$CHBrCH$_3$ (ca. 50%)
+ p-ClC$_6$H$_4$N(CN)CH(CH$_2$)$_3$Br § (ca. 10%)
CH$_3$

N—CN (27%)

Note: References 85–112 are listed on p. 262.
† The product was isolated as the piperidine derivative.
‡ The product was poorly characterized.
§ The primary bromide was isolated as its reaction product with diethylamine.

TABLE IV—*Continued*

CYCLIC AMINES

B. Five-Membered Rings—Continued

Amine	Products	Reference
C₁₁–C₁₃		
(structure) NCH₂CH=CH₂	(structure) NCN (40%) + CH₂=CHCHCl₂Br†	53
CH₃ NC₄H₉	C₄H₉N(CN)(CH₂)₃CHBrCH₃ (ca. 50%) + C₄H₉N(CN)CH(CH₃)₃Br § (ca. 10%) CH₃	50
CH₃ NC₄H₄OCH₃-p	p-CH₃OC₆H₄N(CN)(CH₂)₃CHBrCH₃ (ca. 45%) + p-CH₃OC₆H₄N(CN)CH(CH₃)₃Br § (ca. 15%) CH₃	50
(structure) NC₆H₄OCH₃-o	(structure) NCN + o-CH₂=CHC₆H₄CH₂Br	49
(structure) NCH₂C₆H₅	(structure) NCN + C₆H₅CH₂Br† + o-BrCH₂C₆H₄CH₂N(CN)CH₂C₆H₅	53
C₁₃–C₃₄		
(structure) NCH₂C₆H₄CH₃-p (CO₂C₂H₅)₂	No definite products	92

$C_6H_5CH_2N$ [bicyclic structure] $NCH_2C_6H_5$ → [bicyclic structure] NCN (97%) — 52

C. Six- and Seven-Membered Rings

C_5–C_8

[morpholine, NCH_3] → $CH_3N(CN)CH_2CH_2OCH_2CH_2Br$ + amine hydrobromide — 62

[piperazine, H_3CN ... NCH_3] → $CH_2=CHN(CN)CH_3$ + amine hydrobromide — 64

[cyclohexane, NCH_3] → NCN + $\left[\text{[bicyclic]} N(CH_3)_2\right]$ Br — 93

[cyclohexane, NC_2H_5] → NCN (66%) + $C_2H_5N(CN)(CH_2)_6Br$ — 3, 48

[cyclohexane, NCH_2CN] → NCN + $BrCH_2CN$ (70%) — 3, 79

[cyclohexane, NC_3H_7-n] → NCN (40%) + n-$C_3H_7N(CN)(CH_2)_5Br$ (60%) — 3, 48

[bicyclic, NCH_3] → NCN + $\left[\text{[bicyclic]} N(CH_3)_2\right]$ Br (ca. 50%) — 48, 69

Note: References 85–112 are listed on p. 262.
‡ The products were poorly characterized.
§ The primary bromide was isolated as its reaction product with diethylamine.

TABLE IV—*Continued*

CYCLIC AMINES

C. Six- and Seven-Membered Rings—Continued

Amine	Products	Reference
C₇–C₅	NCN, CH₂CH₂CH₂Br	54
(with CH₃)	NCN, CH₂CH₂CHBrCH₃	54
(with CH₃ CH₃)	NCN, CH(CH₃)CH₂CH₂Br	54
benzoxazine, N-CH₃	[benzoxazine (CH₃)₂ Br] + benzoxazine CN	63
NCH(CN)C₂H₅	No definite products	79

C₉–C₁₁ structure with H₃C and NCH(CH₃)₂	(H₃C) cyclohexane–NCN + amine hydrobromide	56
NC₄H₉-n	n-C₄H₉N(CN)(CH₂)₅Br	7
NC₅H₁₁-i	i-C₅H₁₁N(CN)(CH₂)₅Br	7
NCH₂CH₂CO₂C₂H₅	NCN + CH₂=CHCO₂C₂H₅ + amine hydrobromide (43%)	3
tetrahydroquinoline N–CH₃	quinoline CN product + quinoline (CH₃)₂ Br product	58, 94
NCH(CN)C₄H₉-n	No definite products	79
NC₆H₅	C₆H₅N(CN)(CH₂)₅Br	7, 57
NC₆H₄Br-p	p-BrC₆H₄N(CN)(CH₂)₅Br	7
[N—CH₂]₂	cyclohexane NCN	44

Note: References 85–112 are listed on p. 262.

TABLE IV—*Continued*

CYCLIC AMINES

C. *Six- and Seven-Membered Rings—Continued*

Amine	Products	Reference
C_{11}-C_{13} (bicyclic ring, N—C_2H_5)	(ring, N—CN) (75%) + $C_6H_5N(CN)C_2H_5$ + $CH_2CH_2CH_2Br$	58
(seven-membered bicyclic ring, N—CH_3)	(ring, N—CN)	63
(tetrahydroquinoline, N—C_3H_7-n)	(tetrahydroquinoline, N—CN) + $C_6H_5N(CN)C_3H_7$-n + $CH_2CH_2CH_2Br$	58
CH_3CHN ... O, (tetrahydroquinoline, N—CH_3)	(tetrahydroquinoline, N—CN), CH_3CHN ... O, p-$CH_3C_6H_4N(CN)(CH_2)_5Br$	95
$NC_6H_4CH_3$-p (piperidine)		7

60

60

96

62

79

92

$C_3H_7\text{-}n$

N
|
CH$_3$

$C_3H_7\text{-}n$

N
|
CH$_3$

NCH$_2$C$_6$H$_5$

NCH$_2$C$_6$H$_4$C$_2$H$_5$-o

NCH(CN)C$_6$H$_{13}$-n

C$_{14}$–C$_{16}$

NCH$_2$C$_6$H$_4$CH$_3$-p

$C_3H_7\text{-}n$

N
|
CN

N(CN)CH$_3$

CH=CHCHBrC$_3$H$_7$-n

NCN + C$_6$H$_5$CH$_2$Br

NCN + o-C$_2$H$_5$C$_6$H$_4$CH$_2$Br

No definite products

NCN (ca. 50%) + p-CH$_3$C$_6$H$_4$CH$_2$Br

Note: References 85–112 are listed on p. 262.
¶ This is the only recorded example of the reaction of cyanogen bromide with a seven-membered cyclic amine.

TABLE IV—*Continued*

CYCLIC AMINES

Products

C. Six- and Seven-Membered Rings—Continued

Amine	Products	Reference
C_{14}–C_{14} (*Cont'd*)		
⬡NCH₂CH₂CH₂OC₆H₅	$C_6H_5OCH_2CH_2CH_2N(CN)(CH_2)_5Br$ (ca. 50%) + $C_6H_5OCH_2CH_2CH_2Br$	3
⬡NCH₂C₆H₄CH=CH₂-*o*	⬡NCN + *o*-CH₂=CHC₆H₄CH₂Br	49
⬡NCH₂C₆H₄C₂H₅-*o*	⬡NCN + *o*-C₂H₅C₆H₄CH₂Br	55
⬡NCH₂C₆H₄CH₃-*p* (bicyclic with O)	No definite products	92
quinoline with C₆H₅ and CH₃	tetrahydroquinoline with C₆H₅ and N—CN	59
quinoline with C₆H₅ and CH₃	C₆H₅N(CN)CH₃ (ca. 50%) + CH₂CH₂CHBrC₆H₅	59

D. Pyridine-Type Amines

Amine	Hypothetical Intermediate	Products	Remarks **	Reference
C_5–C_9 (pyridine)	(pyridine intermediate with Br, CN)	ArNHCH=CHCH=CHCH=NAr·HBr	Reaction product of pyridine with cyanogen bromide was treated with an arylamine	97, 98, 99
(quinoline)	(quinoline intermediate with Br, CN)	(quinoline with OH, CN) + (quinoline dimer with CN)$_2$	Water present in reaction mixture	67, 68, 69
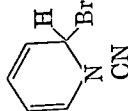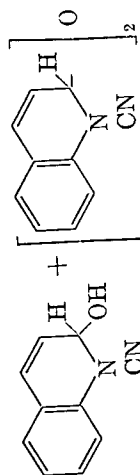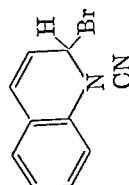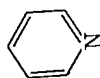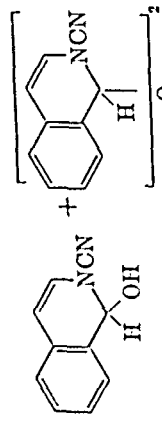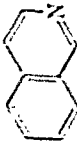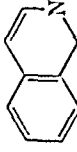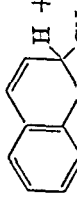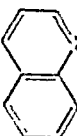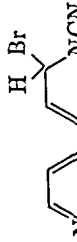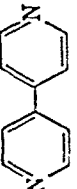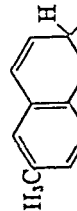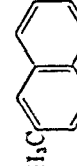
Note: References 85–112 are listed on p. 262.

** See pp. 218–219 for a description of the reactions involved in Table IVD.

TABLE IV—Continued

Cyclic Amines

D. Pyridine-Type Amines—Continued

Amine	Hypothetical Intermediate	Products	Remarks	Reference
C_9-C_{13} (isoquinoline)			Water present in reaction mixture	94
(quinoline)		+ amine hydrobromide	Simultaneous reaction with HCN	70
(4,4'-bipyridine)				65
(methylquinoline, H_3C)		+ amine hydrobromide	Simultaneous reaction with HCN	70

			Reference
(6-methoxyquinoline)	(2-Br-1,2-dihydro) CH_3O — H, Br; N–CN	H, CN; N–CN + amine hydrobromide	Simultaneous reaction with HCN	68
(2-methylquinoline)	CH_3, H, Br; N–CN	CH_3, H, CN; N–CN + amine hydrobromide	Simultaneous reaction with HCN	68
(methyl-substituted)	Br; N–CN; CH_3	H, CN; N–CN; CH_3 + amine hydrobromide	Simultaneous reaction with HCN	68
(phenanthroline type)		Structure not given	Simultaneous reaction with HCN	68
C_{13}–C_{15} (benzoquinoline)		Structure not given	Simultaneous reaction with HCN	70

Note: References 85–112 are listed on p. 262.

TABLE IV—*Continued*

CYCLIC AMINES

Products

D. *Pyridine-Type Amines—Continued*
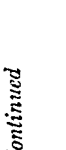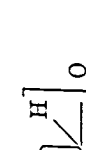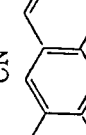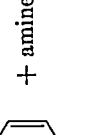
Amine	Hypothetical Intermediate	Products	Remarks	Reference
C_{17} C_{18} (*Cont'd*)			Water present in reaction mixture	68
		Structure not given		68
		+ amine hydrobromide	Simultaneous reaction with HCN	68

TABLE V

ALKALOIDS

Amine	Products	Reference

Amine C_8-C_{15}

Retronecanol

Products: structure with OH, CH(CH$_3$)CH$_2$CH$_2$Br, N–CN

Reference 99a

Lupinane (CH$_3$)

Product: piperidine with CH$_3$, (CH$_2$)$_4$Br, N–CN
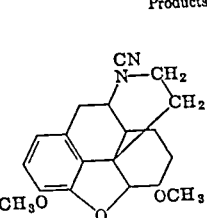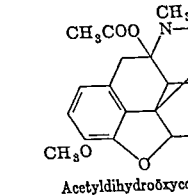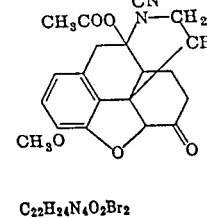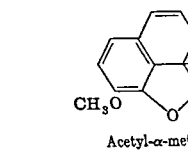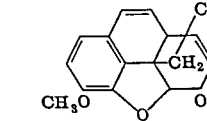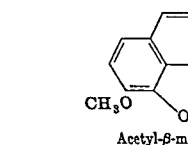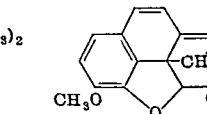
Reference 76

Anhydroecgonine methyl ester, CO$_2$CH$_3$

Product: NCN*, CO$_2$CH$_3$

Reference 78

Hydrobydrastinine, H_2C, NCH$_3$

Product: H_2C, CH$_2$CH$_2$N(CN)CH$_3$, CH$_2$Br (ca. 55%)

+ quaternary salt (ca. 45%)

Reference 61

Hydrocotarnine, H_2C, NCH$_3$, OCH$_3$

Product: H_2C, CH$_2$CH$_2$N(CN)CH$_3$, CH$_2$Br (ca. 25%), OCH$_3$

+ quaternary salt

Reference 61

$C_{15}H_{24}N_2O$
Lupanine

$C_{16}H_{24}N_3O_2Br$

Reference 100, 101

$C_{15}H_{26}N_2$
Sparteine

$C_{17}H_{26}N_4Br_2 + C_{16}H_{26}N_3Br$ (two isomers)

Reference 77

Cocaine, C_6H_5COO, NCH$_3$, CO$_2$CH$_3$

Product: C_6H_5COO, NCN (ca. 60%), CO$_2$CH$_3$

Reference 78

C_{17}-C_{20}
2,3-Diketonucidine

$C_{18}H_{20}N_3O_3Br$ (80%) + $C_{35}H_{40}N_5O_6Br$ (7.5%)

Reference 102

Thebaine

Product: structure with Br, CH$_2$CH$_2$N(CN)CH$_3$, CH$_3$O, OCH$_3$, O

Reference 74

Note: References 85–112 are listed on p. 262.
* Considerable ring cleavage occurred, and the yield of the product shown was small. See p. 223.
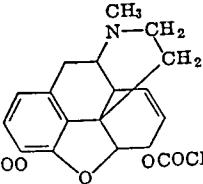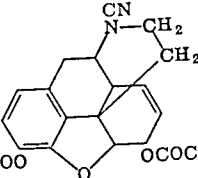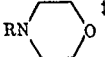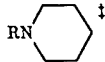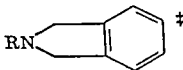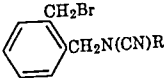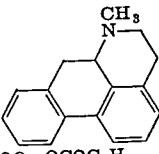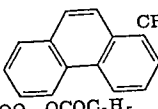
TABLE V—*Continued*

ALKALOIDS

Amine	Products	Reference

C₁₇–C₂₀ *(Con't)*
Tetrahydrothebaine

74

$C_{20}H_{28}N_3O_2 \cdot 2HBr$

$C_{19}H_{22}N_2O$
Cinchonine

103

$C_{20}H_{22}N_3OBr$

104

$C_{19}H_{22}N_2O$
Cinchonidine

105

Acetyldihydroöxycodeinone

$C_{20}H_{24}N_2O_2$
Quinine

$C_{22}H_{24}N_4O_2Br_2$

104

$C_{20}H_{24}N_2O_2$
Quinidine

$C_{22}H_{24}N_4O_2Br_2$

103

C₂₁

Addition product of undetermined composition

106

$C_{21}H_{22}N_2O_2$
Strychnine

$C_{21}H_{24}N_2O$
Strychnidine

$C_{22}H_{24}N_3OBr + (C_{22}H_{24}N_3OBr)_2$

102

74

Acetyl-α-methylmorphimethine

107

Acetyl-β-methylmorphimethine

Note: References 85–112 are listed on p. 262.

TABLE V—*Continued*

ALKALOIDS

Amine	Products	Reference

C_{21} *(Con't)*

Diacetylmorphine

(ca. 75%)

74

C_{22}–C_{25}

RN O ‡

$RN(CN)CH_2CH_2OCH_2CH_2Br$

108

RN ‡

$RN(CN)(CH_2)_5Br$

108

$C_{23}H_{26}N_2O_4$
Brucine

$C_{24}H_{26}N_3O_4Br + C_{47}H_{52}N_6O_8Br$

102, 106, 109, 110

$C_{23}H_{28}N_2O_4$
Dihydrobrucine

$C_{24}H_{28}N_3O_4Br$

109, 110

$C_{24}H_{40}N_2$
Conessine

$C_{24}H_{37}N_3 + C_{26}H_{46}N_2Br_2 + C_{24}H_{34}N_4 + $ conessine hydrobromide

73

$C_{24}H_{40}N_2$
Isoconessine

$C_{24}H_{37}N_3 + C_{26}H_{46}N_2Br_2 + C_{24}H_{34}N_4 + $ isoconessine hydrobromide

111

RN ‡

CH_2Br
$CH_2N(CN)R$

108

C_{26}–C_{31}
Acetylphenyldihydrothebaine

$C_{27}H_{26}N_2O_4$

112

$CH_2CH_2N(CN)CH_3$

C_6H_5COO $OCOC_6H_5$

75

C_6H_5COO $OCOC_6H_5$
Dibenzoylapomorphine

Note: References 85–112 are listed on p. 262.

‡ R =

CH_2CH_2—

CH_3O O $OCOCH_3$
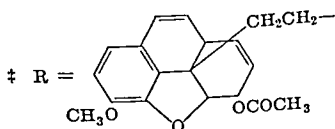
REFERENCES TO TABLES II–V

[85] Ochiai and Tsuda, *J. Pharm. Soc. Japan*, **56**, 357 (1936) [*C. A.*, **30**, 6363 (1936)].

[86] von Braun and Moldaenke, *Ber.*, **56**, 2165 (1923).

[87] Sachs and Weigert, *Ber.*, **40**, 4356 (1907).

[83] von Braun, *Ber.*, **37**, 2670 (1904).

[89] von Braun and Tauber, *Ann.*, **458**, 102 (1927).

[90] von Braun and Aust, *Ber.*, **49**, 993 (1916).

[91] von Braun, *Ber.*, **37**, 633 (1904).

[92] von Braun and Leistner, *Ber.*, **59**, 2323 (1926).

[93] von Braun, *Ber.*, **33**, 2734 (1900).

[94] Shimidzu, *J. Pharm. Soc. Japan*, **537**, 943 (1926) [*C. A.*, **21**, 2694 (1927)].

[95] von Braun, Grabowski, and Rawicz, *Ber.*, **46**, 3179 (1913).

[96] von Braun and Seemann, *Ber.*, **56**, 1840 (1923).

[97] Knunyants and Kefeli, *J. Gen. Chem. U.S.S.R.*, **15**, 628 (1945) [*C. A.*, **40**, 6079 (1946)].

[93] König, *J. prakt. Chem.*, [2] **69**, 105 (1904).

[99] König, *J. prakt. Chem.*, [2] **70**, 19 (1904).

[99a] Adams, Carmack, and Mahan, *J. Am. Chem. Soc.*, **64**, 2593 (1942).

[100] Winterfeld and Kneuer, *Ber.*, **64**, 150 (1931).

[101] Thoms and Bergerhoff, *Arch. Pharm.*, **263**, 3 (1925).

[102] Leuchs and Overberg, *Ber.*, **65**, 961 (1932).

[103] Shimidzu, *J. Pharm. Soc. Japan*, **543**, 370 (1927) [*C. A.*, **21**, 3055 (1927)].

[104] Shimidzu, *J. Pharm. Soc. Japan*, **48**, 31 (1928) [*C. A.*, **22**, 1780 (1928)].

[105] Speyer and Sarre, *Ber.*, **57**, 1427 (1924).

[106] Mossler, *Monatsh.*, **31**, 1 (1910).

[107] von Braun and Cahn, *Ann.*, **451**, 72 (1926).

[103] von Braun, *Ber.*, **52**, 1999 (1919).

[109] Wieland and Gumlich, *Ann.*, **494**, 197 (1932).

[110] Leuchs and Overberg, *Ber.*, **66**, 79 (1933).

[111] Siddiqui and co-workers, *Proc. Indian Acad. Sci.*, **4A**, 283 (1936) [*C. A.*, **31**, 1027 (1937)].

[112] Freund and Speyer, *Ber.*, **49**, 1306 (1916).

CHAPTER 5

HYDROGENOLYSIS OF BENZYL GROUPS ATTACHED TO OXYGEN, NITROGEN, OR SULFUR

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and

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CONTENTS

INTRODUCTION

The benzyl group and a variety of substituted benzyl groups attached to an oxygen atom as in alcohols, ethers, acetals, or esters; to an amino nitrogen atom; or to a sulfur atom in thio ethers may be removed as toluene, or the correspondingly substituted toluene, by hydrogenolysis.

$$ArCH_2OH + H_2 \rightarrow ArCH_3 + H_2O$$

$$ArCH_2OR + H_2 \rightarrow ArCH_3 + ROH$$

$$ArCH(OR)_2 + 2H_2 \rightarrow ArCH_3 + 2ROH$$
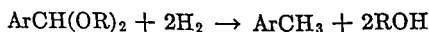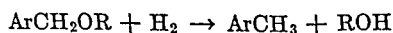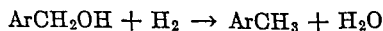
application is the synthesis of phenylacetic acid from the acetate of mandelic acid.

$$C_6H_5CHCO_2H + H_2 \rightarrow C_6H_5CH_2CO_2H + CH_3CO_2H$$
$$| $$
$$OCOCH_3$$
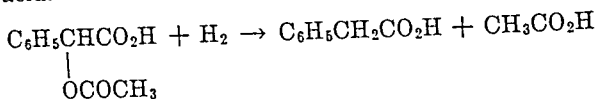
It is the purpose of this chapter to give illustrations of both types of debenzylations so that the usefulness of the reactions may be better appreciated and their applications extended. Since most descriptions of debenzylations in the literature are subordinated to other aspects of the studies in which they are reported, it is certain that not all of the examples of the reaction have been found and discussed in the text or listed in the tables.

SCOPE AND LIMITATIONS

Substituents may be present in the methylene side chain or in the nucleus of the benzyl group. The effects of the various substituents, in either the methylene or the phenyl group, are best considered under the various types of debenzylations as discussed in the following subsections: removal of the benzyl attached to oxygen, to nitrogen, or to sulfur.

The role of the benzyl group may also be taken by the benzhydryl [14] or the triphenylmethyl [15] group.

$$RNHCH(C_6H_5)_2 \xrightarrow{H_2} RNH_2 + CH_2(C_6H_5)_2$$

$$\begin{array}{ccc} CH_2OC(C_6H_5)_3 & & CH_2OH \\ | & & | \\ CH_3CO_2CH & & CH_3CO_2CH \\ | & \xrightarrow{H_2} & | \\ CH_3CO_2CH & & CH_3CO_2CH \\ | & & | & + 2CH(C_6H_5)_3 \\ HCOCOCH_3 & & HCOCOCH_3 \\ | & & | \\ HCOCOCH_3 & & HCOCOCH_3 \\ | & & | \\ CH_2OC(C_6H_5)_3 & & CH_2OH \end{array}$$
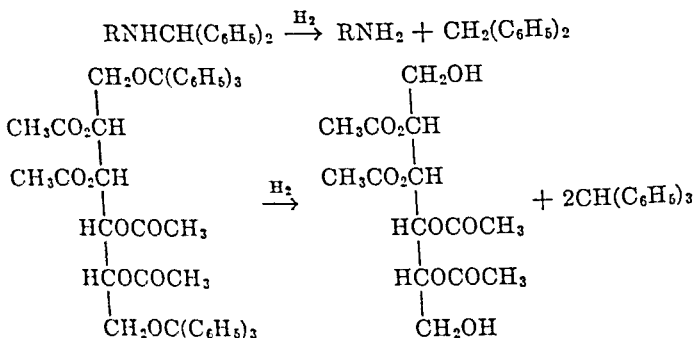
Hydrogenolysis may be accomplished by either chemical or catalytic means. Palladium seems to be the favored catalyst, but platinum, nickel, and copper chromium oxide have also been used successfully. No study of their relative merits has appeared. Chemical debenzylations have been effected by Raney nickel alloy, sodium amalgam, sodium in liquid ammonia, and lithium aluminum hydride.

[14] Suter and Ruddy, *J. Am. Chem. Soc.*, **66**, 747 (1944).
[15] Michael, *Ber.*, **65**, 262 (1932).

Cleavage of the Benzyl-Oxygen Bond

Alcohols, aldehydes, and ketones (Tables I, II, III, and IV). Benzyl alcohol is rapidly and quantitatively reduced to toluene. Nuclear-substituted benzyl alcohols behave similarly. p-Methoxybenzyl alcohol in ethanolic solution on reduction with palladium on charcoal forms p-methylanisole,[16] and salicin reduced with colloidal platinum,[17] platinum black, or palladium black [18] furnishes o-tolylglucoside.

$$p\text{-}CH_3OC_6H_4CH_2OH + H_2 \rightarrow p\text{-}CH_3OC_6H_4CH_3 + H_2O$$
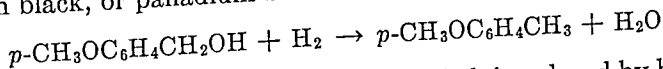
Cinnamyl alcohol, a vinylog of benzyl alcohol, is reduced by hydrogen and palladium-carbon catalyst to a mixture of n-propylbenzene and 3-phenyl-1-propanol.[16] It is probable, by analogy with information on nuclear hydrogenation,[19] that these products result from competing and not from successive reactions: hydrogenation of the ethylenic bond to furnish the alcohol and "decinnamylation" by hydrogenolysis, followed by reduction of the double bond to furnish propylbenzene.

$$C_6H_5CH{=}CHCH_2OH \nearrow C_6H_5CH_2CH_2CH_2OH$$
$$\searrow (C_6H_5CH{=}CHCH_3) \rightarrow C_6H_5CH_2CH_2CH_3$$
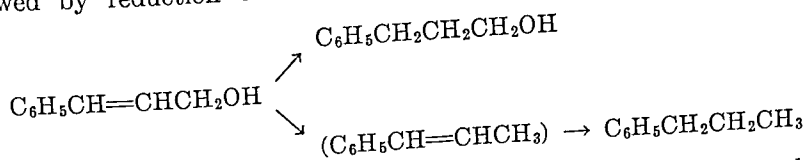
Benzyl alcohols substituted in the α position likewise undergo hydrogenolysis. 1-Phenyl-1-propanol is reduced to propylbenzene,[20] 1-phenyl-1-ethanol forms ethylbenzene,[21] 1-phenylethane-1,2-diol yields phenethyl alcohol, and diphenylcarbinol is converted to diphenylmethane.[16]

Since aldehydes of the general formula ArCHO may be reduced to the corresponding benzyl alcohols, ArCH$_2$OH, and ketones of general structure ArCOR form α-substituted benzyl alcohols, ArCHROH, it is to be expected that many aldehydes and ketones may be reduced directly to the corresponding toluenes or alkylbenzenes without the isolation of the intermediate alcohol. This expectation is realized in practice.[16, 20, 22, 23] Many aldehydes and ketones have been reduced at room temperature and low pressures to the corresponding hydrocarbons with hydrogen and palladium-carbon or copper chromium oxide cata-

[16] Baltzly and Buck, *J. Am. Chem. Soc.*, **65**, 1984 (1943).
[17] Kariyone and Kondo, *J. Pharm. Soc. Japan*, **48**, 684 (1928) [*C. A.*, **23**, 393 (1929)].
[18] Richtmyer, *J. Am. Chem. Soc.*, **56**, 1633 (1934).
[19] Van Duzee and Adkins, *J. Am. Chem. Soc.*, **57**, 147 (1935).
[20] Hartung and Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).
[21] Kindler, Scharfe, and Henrich, *Ann.*, **565**, 51 (1949).
[22] Hartung and co-workers, unpublished results.
[23] Hartung and Smith, *J. Elisha Mitchell Society*, **66**, 171 (1950) [*C. A.*, **47**, 2716 (1953)].

lysts (Table III). Similar results may be accomplished by using Raney nickel-aluminum alloy and alkali.[24]

If the aryl alkyl ketone contains a phenolic hydroxyl in the *ortho* position, reduction to the hydrocarbon derivative does not take place. *o*-Hydroxypropiophenone is not reduced by palladium-carbon catalyst, and the 4-acylresorcinols are not reduced to the corresponding alkyl-resorcinols by either palladium or Raney nickel.[22] For such reductions the Clemmensen[25] or the Wolff-Kishner[26] reactions must be used. Also complete substitution in the α position of the aryl alkyl ketone inhibits hydrogenolysis. Pivalophenone, $C_6H_5COC(CH_3)_3$, is smoothly and quantitatively reduced to the carbinol but not to the hydrocarbon.[16] The same behavior may be expected from other aryl *t*-alkyl ketones.

The hydrochlorides of aryl α-aminoalkyl ketones, $ArCOCHRNH_3Cl$, are reduced only to the amino alcohol when palladium catalyst is employed; however, if the amino ketone or the amino alcohol is hydrogenated in acetic acid at 80–90° with palladium on barium sulfate in the presence of perchloric acid, excellent yields of the desoxy compound are obtained.[27] It is suggested that in the presence of perchloric acid the reduction proceeds through the acetic acid ester of the amino alcohol.

$$\begin{array}{c} ArCOCHRNH_3Cl \\ H_2 \downarrow Pd \\ ArCHOHCHRNH_3Cl \end{array} \quad \underset{CH_3CO_2H}{\xrightarrow{Pd, H_2, HClO_4}} \quad ArCH_2CHRNH_3Cl$$
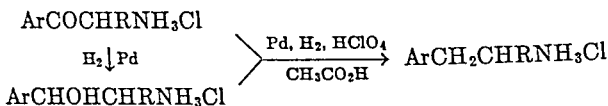
An extension of the development described in the preceding paragraph is the reduction in one step, by means of palladium catalyst in acetic acid-perchloric acid solution, of α-oximino ketones to the corresponding amines.[27] The reduction of benzaldehyde cyanohydrin to phenethyl-

$$ArCOC(R)=NOH \rightarrow ArCH_2CHRNH_2$$
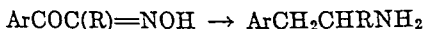
amine does not require the presence of acetic or perchloric acid but proceeds in ethanolic hydrogen chloride solution.[28]

The reduction of esters of aromatic acids to the corresponding hydrocarbons by means of copper chromium oxide[29] occurs by virtue of the

$$ArCO_2C_2H_5 + 3H_2 \rightarrow ArCH_3 + C_2H_5OH + H_2O$$
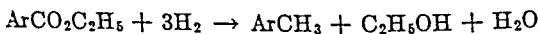
fact that these esters are first reduced to the aromatic alcohols, and the alcohol then undergoes hydrogenolysis. Ethyl benzoate, for example, reduced with copper chromium oxide in methanolic solution at 300 atm.

[24] Papa, Schwenk, and Whitman, *J. Org. Chem.*, **7**, 587 (1942).
[22] Martin, in Adams, *Organic Reactions*, Vol. I, p. 155, John Wiley & Sons, 1942.
[25] Todd, in Adams, *Organic Reactions*, Vol. IV, p. 378, John Wiley & Sons, 1948.
[26] Rosenmund and Karg, *Ber.*, **75**, 1850 (1942).
[25] Hartung, *J. Am. Chem. Soc.*, **50**, 3370 (1928).
[29] Lazier, U. S. pat. 2,079,414 [*C. A.*, **31**, 4340 (1937)].

and 125–175° is converted to benzyl alcohol.[30]   If the temperature is increased to 200–250°, the products of the reaction are toluene, ethanol, and water.[31]

The ability of lithium aluminum hydride to effect hydrogenolysis of benzyl alcohols bearing an amino substituent in the *ortho* or *para* position is a recent discovery.[32]   Since this reducing agent converts esters, aldehydes, or ketones to carbinols,[32a] it is seen that appropriately substituted intermediates may be converted directly to the corresponding toluidines.   Illustrative of this reaction are the conversion of methyl anthranilate to *o*-toluidine (39%), *o*-aminobenzyl alcohol to *o*-toluidine (53%), *p*-aminobenzoic acid to *p*-toluidine (47%), *p*-dimethylamino-benzaldehyde to N,N-dimethyl-*p*-toluidine (78%), and *p*-aminobenzo-phenone to *p*-aminodiphenylmethane (57%).

Ethers (Table V). Hydrogenolysis of benzyl ethers proceeds smoothly, and the yields of products are generally good.   Nickel or platinum catalysts may be used, but palladium is preferred if hydrogenation of the nucleus is to be avoided.

Benzyl alkyl ethers are quantitatively reduced to toluene and the corresponding alcohol by palladium [12] or by Raney nickel.[19]   Benzyl phenyl ether is converted into toluene and phenol when palladium-charcoal catalyst is used; [11] but with Raney nickel as catalyst at 100° and 150–200 atm. toluene and both phenol and cyclohexanol are formed.[19]

The hydrogenolyses described in the preceding section, where the benzyl group is retained in the product desired, have their parallel in certain oxygen heterocycles containing an α-phenyl substituent, for example, the conversion of 2-phenyltetrahydropyran into 5-phenyl-1-pentanol and of phenyldioxane into phenethyl β-hydroxyethyl ether.[33]

$$\rightarrow C_6H_5(CH_2)_5OH$$

$$\rightarrow C_6H_5CH_2CH_2OCH_2CH_2OH$$
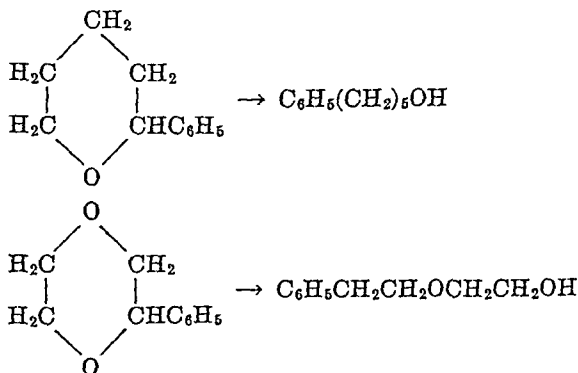
[30] Mozingo and Folkers, *J. Am. Chem. Soc.*, **70**, 229 (1948).

[31] Adkins, *Reactions of Hydrogen*, pp. 97–104, University of Wisconsin Press, 1937.

[32] Conover and Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950).

[32a] Brown, in Adams, *Organic Reactions*, Vol. VI, p. 469, John Wiley & Sons, 1951.

[33] Baker, Cornell, and Cron, *J. Am. Chem. Soc.*, **70**, 1490 (1948).

The principal application of the hydrogenolysis of benzyl ethers is in removing a benzyl group introduced earlier in order to protect a hydroxyl group during a series of reactions. For example, 1-(3-methoxy-4-benzyloxyphenyl)-2-acetaminopropanol (I) may be cyclized to the isoquinoline derivative II and the benzyl group then removed by hydrogenolysis to liberate the hydroxyl group in the 7 position of the isoquinoline III.[34] 6,7-Dihydroxy-1-(3',4'-methylenedioxybenzyl)isoquinoline (IV) may be prepared in an analogous manner.[35]
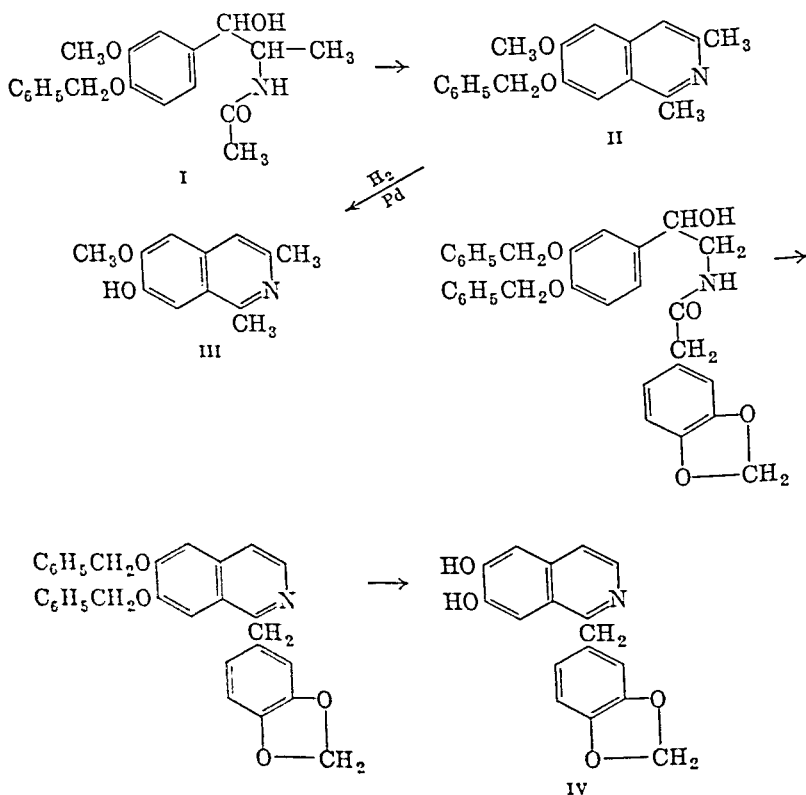
For the preparation of 3-(7-hydroxy-n-heptyl)veratrole (V) the Grignard reagent from 6-benzyloxy-1-bromohexane was allowed to react with 2,3-dimethoxybenzaldehyde to form a carbinol, which was dehydrated; reduction of the unsaturated intermediate in acetic acid solu-

tion with palladium black saturated the double bond and simultaneously removed the benzyl group.[36]

$$\underset{\substack{\text{CHO}}}{C_6H_3(OCH_3)_2} + BrMg(CH_2)_6OCH_2C_6H_5 \rightarrow \underset{\substack{\text{CHOH(CH}_2)_6OCH_2C_6H_5}}{C_6H_3(OCH_3)_2} \xrightarrow{-H_2O}$$

$$\underset{\substack{\text{CH}=CH(CH_2)_5OCH_2C_6H_5}}{C_6H_3(OCH_3)_2} \xrightarrow{H_2} \underset{\substack{\text{CH}_2(CH_2)_6OH \\ V}}{C_6H_3(OCH_3)_2}$$
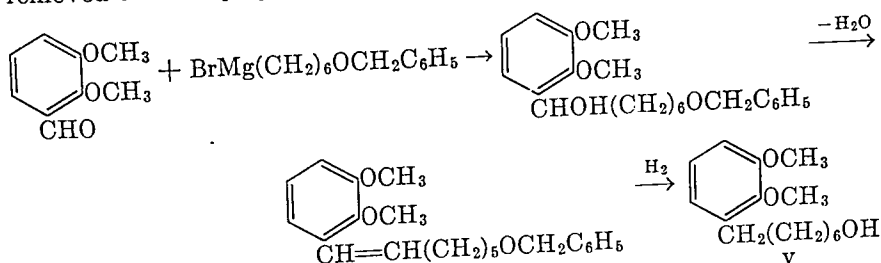
The benzyloximino compounds are also useful in masking oximes because of the ease with which the protecting benzyl group may be removed by hydrogenolysis. α-Oximino acids cannot be converted into their corresponding acid chlorides, but the O-ethers, the alkyloximino acids, are conveniently available and can be converted in good yields into the corresponding acid chlorides by the usual methods.[37] The α-benzyloximino acid chlorides react with α-amino acids to form amides (VI) which may be reduced to dipeptides; [38] and the acid chloride will react with a dipeptide to form an attractive intermediate (VII) for the synthesis of a tripeptide.[39]

$$\underset{\substack{\text{NOCH}_2C_6H_5}}{RCCOCl} \xrightarrow{NH_2CH_2CONHCH_2CO_2H} \underset{\substack{\text{NOCH}_2C_6H_5 \\ VII}}{RCCONHCH_2CONHCH_2CO_2H}$$

$$\downarrow NH_2CHR'CO_2H \qquad\qquad H_2\downarrow Pd$$

$$\underset{\substack{\text{NOCH}_2C_6H_5 \\ VI}}{RCCONHCHR'CO_2H} \qquad RCH(NH_2)CONHCH_2CONHCH_2CO_2H$$

$$H_2\downarrow Pd$$

$$RCH(NH_2)CONHCHR'CO_2H$$
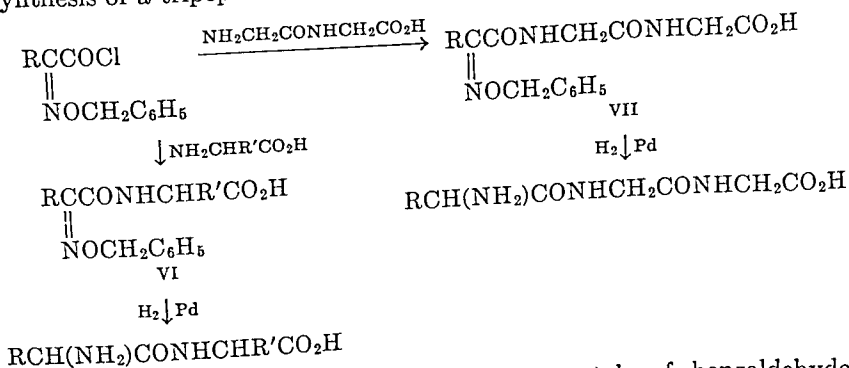
Acetals (Table VI). Hydrogenolysis of acetals of benzaldehyde furnishes toluene and the alcohol from which the acetal was formed.[10,40]

$$C_6H_5CH(OR)_2 \xrightarrow{H_2} C_6H_5CH_3 + 2ROH$$
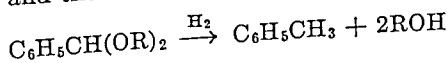
[36] Wasserman and Dawson, *J. Org. Chem.*, **8**, 73 (1943).
[37] Waters and Hartung, *J. Org. Chem.*, **12**, 469 (1947).
[38] Weaver and Hartung, *J. Org. Chem.*, **15**, 741 (1950).
[39] Kramer, Hartung, and Hager, Chicago Meeting, American Chemical Society, September 1950.
[40] Sigmund, *Monatsh.*, **53–54**, 607 (1929).

The reaction is useful for the preparation of otherwise inaccessible esters of certain polyhydroxy compounds, for example, the β-monoglycerides.[41] Glycerol and benzaldehyde form the 1,3-diacetal, leaving the secondary alcoholic group available for esterification; hydrogenolysis of the benzal group affords toluene and the β-glyceride. The benzaldehyde acetals of

$$C_6H_5CH \begin{matrix} OCH_2 \\ \diagup \quad \diagdown \\ \diagdown \quad \diagup \\ OCH_2 \end{matrix} CHOH \rightarrow C_6H_5CH \begin{matrix} OCH_2 \\ \diagup \quad \diagdown \\ \diagdown \quad \diagup \\ OCH_2 \end{matrix} CHOCOR \xrightarrow{H_2} C_6H_5CH_3 + \begin{matrix} CH_2OH \\ | \\ CHOCOR \\ | \\ CH_2OH \end{matrix}$$
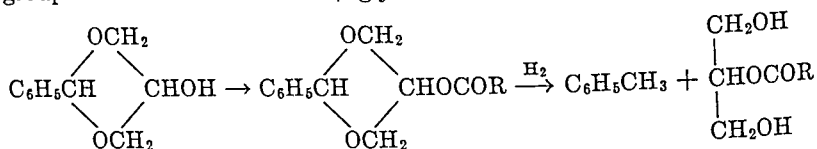
sugars undergo similar hydrogenolyses. Benzal-α-methylglucoside with hydrogen in the presence of platinum sponge forms toluene and α-methylglucoside.[42]
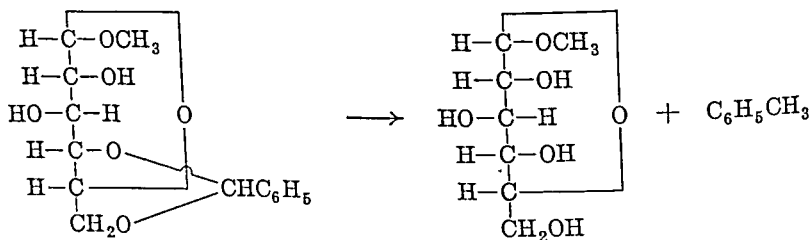
Benzaldehyde diacetate has been reduced to toluene and acetic acid.[7] No practical applications of this type of hydrogenolysis have been reported.

Esters (Tables VII and VIII). Esters of benzyl alcohol are reduced practically quantitatively to toluene and the acid from which the ester is formed.[7,9] The reduction of the acetates of mandelic acid and its nuclear-substituted derivatives to the corresponding arylacetic acids, by means of palladium on barium sulfate and hydrogen, illustrates the type of hydrogenolysis in which the product of interest retains the benzyl group.[43]

$$\begin{matrix} ArCHCO_2H \\ | \\ OCOCH_3 \end{matrix} \rightarrow ArCH_2CO_2H + CH_3CO_2H$$
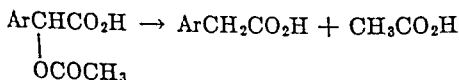
Hydrogenolyses of benzyl esters have also found important use in syntheses in which benzyl groups are employed to protect carboxyl groups and hence are not retained in the final products. Alkaline hydrolysis of an acylated malonic ester such as $RCOCR'(CO_2C_2H_5)_2$ does

⁴¹ Bergmann and Carter, Z. physiol. Chem., **191**, 211 (1930).
⁴² Freudenberg, Toepfer, and Anderson, Ber., **61**, 1750 (1928).
⁴³ Rosenmund and Schindler, Arch. Pharm., **266**, 281 (1928).

not lead to the corresponding malonic acid for the acyl group is hydrolyzed more rapidly than the ester groups.[43a]   The benzyl esters, however, submit smoothly to hydrogenolysis with palladium-charcoal; decarboxylation of the malonic acid affords the ketone.[44]   This method has

$$\begin{array}{c} R' \\ | \\ RCOCCO_2CH_2C_6H_5 \\ | \\ CO_2CH_2C_6H_5 \end{array} \xrightarrow[\text{Pd}]{H_2} \left[\begin{array}{c} R' \\ | \\ RCOCCO_2H \\ | \\ CO_2H \end{array} \right] \rightarrow RCOCH_2R' + 2CO_2$$
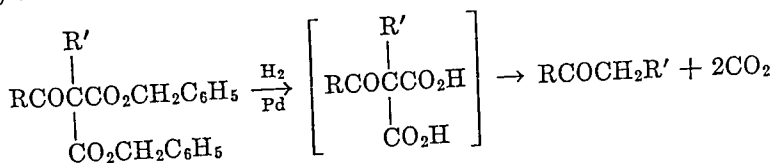
been employed for the synthesis of compounds such as 3-tridecanonoic acid, 8-heptadecanone, 14-ethyl-13-octadecanonoic acid, 11-eicosanon-1-ol, 1-phenyl-2-pentanon-1-ol, and 3-m-methoxybenzoylpropionic acid.

A most attractive use of the debenzylation of esters by hydrogenolysis is the carbobenzyloxy method, developed by Bergmann and Zervas,[45,46] for the synthesis of the peptide linkage.   Carbobenzyloxy chloride, $C_6H_5CH_2OCOCl$, reacts with an amino acid to form a benzyl carbamate, $C_6H_5CH_2OCONHCHRCO_2H$; the free carboxyl group in this product may be converted into an acid chloride function, which by reaction with another molecule of amino acid yields the intermediate for a dipeptide.   Hydrogenolysis forms toluene and a carbamic acid which

$$C_6H_5CH_2OCONHCHRCO_2H \rightarrow C_6H_5CH_2OCONHCHRCOCl \xrightarrow{NH_2CHR'CO_2H}$$

$$C_6H_5CH_2OCONHCHRCONHCHR'CO_2H \xrightarrow{H_2}$$

$$NH_2CHRCONHCHR'CO_2H + C_6H_5CH_3 + CO_2$$
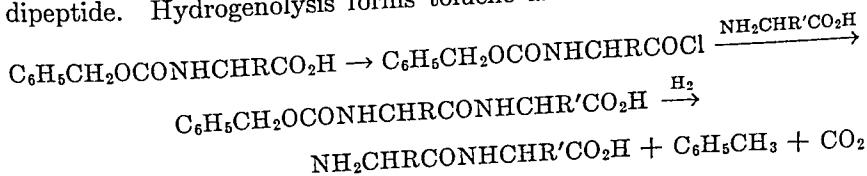
spontaneously loses carbon dioxide, thus liberating the amino group which was protected during formation of the peptide linkage.   The hydrogenolysis is effected by palladium black and hydrogen, and the yields are generally good.   The free carboxyl group of the dipeptide derivative may, via its acid chloride, be coupled with a third amino acid, and so on, debenzylating only at the end of the synthesis.[47]   An indication of the extent to which this reaction has been applied is shown in Table VIII.

The p-bromobenzyl carbamates, prepared from amino acids and p-bromocarbobenzyloxy chloride, have higher melting points and crystallize better than the corresponding benzyl carbamates.   The p-bromo

[43a] The acid hydrolysis and decarboxylation of the acylated malonic ester $C_2H_5O_2$-$CCH_2CH_2COCH(CO_2C_2H_5)_2$ to the acid $HO_2CCH_2CH_2COCH_2CO_2H$ has been carried out by Eisner, Elvidge, and Linstead, *J. Chem. Soc.*, **1950**, 2223.

[44] Bowman, *J. Chem. Soc.*, **1950**, 325.

[45] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

[46] Bergmann and Zervas, *Ber.*, **65**, 1201 (1932).

[47] Barkdoll and Ross, *J. Am. Chem. Soc.*, **66**, 951 (1944).

derivatives undergo hydrogenolysis in the same manner as do the un-halogenated carbamates.[47a]

Because of the mild conditions under which benzyl carbamates respond to hydrogenolysis, certain derivatives lend themselves well for the recovery of pure isomers from a mixture of diastereoisomeric carbamates, thus avoiding the risk of Walden inversion or other chemical reactions which may accompany chemical deacylations. This is illustrated by the separation of the two racemic forms of norephedrine by way of their carbobenzyloxy derivatives.[48] $(+,-)$-Nor-ψ-ephedrine forms a urethane in which the amide group migrates quantitatively from the nitrogen to the oxygen atom, thus permitting easy separation of N-carbobenzyloxy-$(+,-)$-norephedrine from O-carbobenzyloxy-$(+,-)$-nor-ψ-ephedrine. Hydrogenolysis of each derivative regenerates the corresponding racemate.

$$C_6H_5CHOHCHCHCH_3$$
$$|$$
$$NH_2$$

$(+,-)$-Nor-ψ-ephedrine $\quad (+,-)$-Norephedrine

$$C_6H_5CHOHCHCHCH_3 \qquad\qquad C_6H_5CHOHCHCHCH_3$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad |$$
$$NHCO_2CH_2C_6H_5 \qquad\qquad NHCO_2CH_2C_6H_5$$
m.p. 83° $\qquad\qquad\qquad\qquad\qquad$ m.p. 103°

$\downarrow$ H⁺ $\qquad\qquad\qquad\qquad\qquad\qquad \downarrow$ H₂

$$C_6H_5CHCHCHCH_3 \qquad\qquad\qquad C_6H_5CHOHCHCHCH_3$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$NH_3^+ \qquad\qquad\qquad\qquad\qquad\qquad NH_2$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad (+,-)\text{-Norephedrine}$$
$$OCO_2CH_2C_6H_5$$

$\downarrow$ H₂

$$C_6H_5CHOHCHCHCH_3$$
$$|$$
$$NH_2$$
$(+,-)$-Nor-ψ-ephedrine
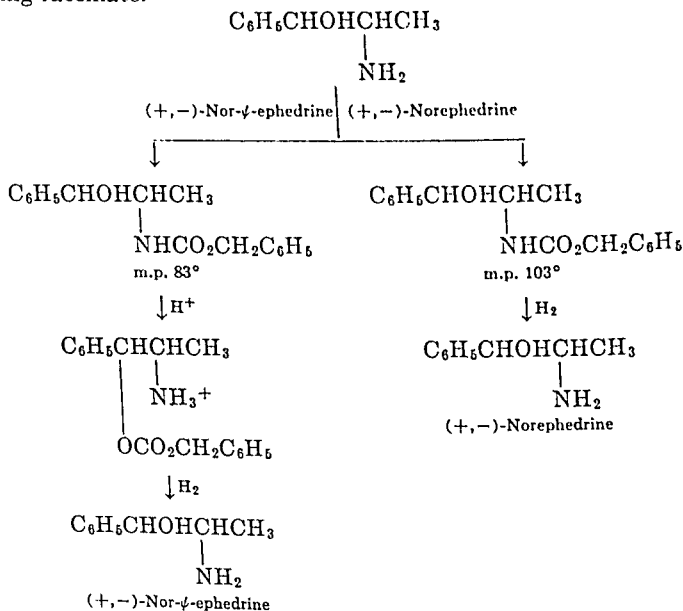
The carbobenzyloxy method promises to be useful for the synthesis of aminoalkylmalonic acids, $NH_2CR(CO_2H)_2$. Aminomalonic ester, first converted into its carbobenzyloxy derivative, can be alkylated; the ethyl ester groups may be removed by milder hydrolysis than the benzyl ester, thus forming a carbobenzyloxyaminoalkylmalonic acid (VIII); the

[47a] Channing, Turner, and Young, *Nature*, **167**, 487 (1951).
[48] Fodor and Kiss, *Nature*, **163**, 287 (1949).

mild conditions of the hydrogenolytic reaction permit reduction of the malonic acid or its salt.[49]

$$C_6H_5CH_2OCONHCH(CO_2C_2H_5)_2 \xrightarrow{\text{Alkylation}}$$

$$C_6H_5CH_2OCONH\overset{\overset{\displaystyle R}{|}}{C}(CO_2C_2H_5)_2 \xrightarrow[\text{hydrolysis}]{\text{Mild alkaline}} C_6H_5CH_2OCONH\overset{\overset{\displaystyle R}{|}}{C}(CO_2H)_2 \xrightarrow{H_2}$$
$$\text{VIII}$$

$$NH_2\overset{\overset{\displaystyle R}{|}}{C}(CO_2H)_2 + C_6H_5CH_3 + CO_2$$
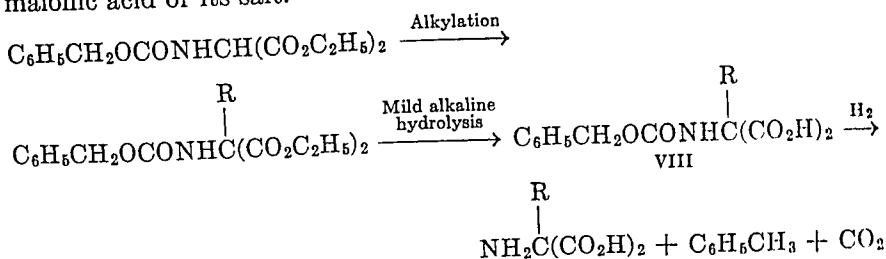
The carbobenzyloxy group can also be removed by chemical means. Carbobenzyloxy-β-alanine, treated with sodium in liquid ammonia, is converted into β-alanine and 1,2-diphenylethane.[50]

$$2C_6H_5CH_2OCONHCH_2CH_2CO_2H \rightarrow$$
$$2NH_2CH_2CH_2CO_2H + C_6H_5CH_2CH_2C_6H_5 + 2CO_2$$
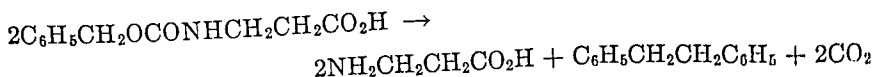
The benzyl esters of phosphoric acid are employed to admirable advantage in the synthesis of phosphorylated amines and alcohols.[50a-e *] The general equations may be summarized as follows.

1. $C_6H_5CH_2OH \xrightarrow{PCl_3} (C_6H_5CH_2O)_2POH \xrightarrow{Cl_2} (C_6H_5CH_2O)_2POCl$

2. $(C_6H_5CH_2O)_2POCl \xrightarrow{R_2NH} (C_6H_5CH_2O)_2PONR_2 \xrightarrow{H_2} R_2NPO_3H_2$

3. $(C_6H_5CH_2O)_2POCl \xrightarrow{HOR} (C_6H_5CH_2O)_2POOR \xrightarrow{H_2} ROPO_3H_2$
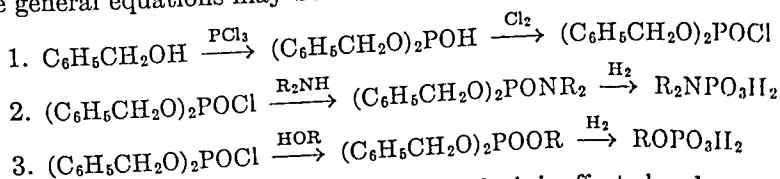
The mild conditions under which hydrogenolysis is effected make possible the synthesis of phosphorylated products of biological significance, which heretofore could be obtained with difficulty or by ambiguous procedures.

Cleavage of Benzyl-Nitrogen Bonds

Amines (Tables IX–XV). Benzylamine, unlike benzyl alcohol, does not readily undergo hydrogenolysis. With palladium oxide [51] or with palladium-charcoal [22] no reduction was observed, and with nickel and

[49] Beaujon, M.S. thesis, University of North Carolina, 1950.
[50] Sifford and du Vigneaud, J. Biol. Chem., 108, 753 (1935).
[50a] Atherton, Openshaw, and Todd, J. Chem. Soc., 1945, 382, 660.
[50b] Atherton and Todd, J. Chem. Soc., 1947, 674.
[50c] Atherton, Howard, and Todd, J. Chem. Soc., 1948, 1106.
[50d] Baddiley, Clark, Michalski, and Todd, J. Chem. Soc., 1949, 815.
[50e] Michelson and Todd, J. Chem. Soc., 1949, 2476, 2487.
* The first example of this use of benzyl esters of phosphoric acid was described by Zervas, Naturwissenschaften, 27, 317 (1939).
[51] Birkofer, Ber., 75, 429 (1942).

hydrogen at high temperatures the hydrogenolysis was slight.[1,2] Secondary amines containing one benzyl and one alkyl group also appear not to undergo hydrogenolysis;[16, 51, 52] in fact, one general method for preparing benzylamines of this type is the catalytic hydrogenation of the intermediate Schiff bases.[52a] The following secondary amines were also found to be resistant to debenzylation: $C_6H_5CH_2NH(CH_2)_3COCH_3$ and $C_6H_5CH_2NH(CH_2)_3CH(CH_3)NH_2$. The latter, however, after conversion to the dimethylamino derivative with formaldehyde and formic acid did cleave at the benzyl-nitrogen bond to form $NH_2(CH_2)_3CH(CH_3)N(CH_3)_2$.[53] The heterocyclic compounds IX and X were stable as hydrochlorides, but the free base IX underwent hydrogenolysis.[53, 54]
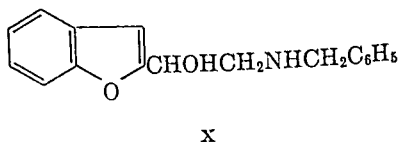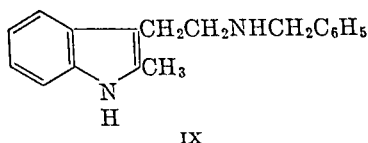
Certain secondary amines containing a benzyl group and an alkyl group which itself carries a non-hydrocarbon substitutent do undergo debenzylation to yield the corresponding primary amine; e.g.,

$C_6H_5CH_2NHCH_2CH_2CO_2H$ [55] $C_6H_5CH_2NHCH(CH_3)CH_2OH$ [56]

$C_6H_5CH_2NHCHCO_2H$ [57] $CH_3(CH_2)_3CH(NHCH_2C_6H_5)CH_2OH$ [58]
$\quad\quad |$
$C_6H_5CH_2NHCHCO_2H$
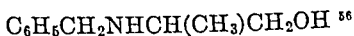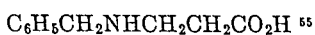
Secondary amines containing an aryl and a benzyl group are readily reduced to toluene and the primary aromatic amines.[7, 13, 51]

Dibenzylamine is resistant to hydrogenolysis; it can in fact be prepared in 97% yield by the reduction of tribenzylamine with palladium oxide.[51] However, dibenzylamines in which one benzyl group is substituted in the aromatic nucleus are amenable to hydrogenolysis, the unsubstituted benzyl group being removed.[16] By means of competitive debenzylation studies (Table XII) of a series of 4,4'-disubstituted

[52] Buck and Baltzly, J. Am. Chem. Soc., 63, 1964 (1941).

[52a] Emerson, in Adams, Organic Reactions, Vol. IV, p. 174, John Wiley & Sons, 1948.

[53] Eisleb and Ehrhart, Ger. pat. 550,762 (Chem. Zentr., 1932 II, 615).

[54] Burger and Deinet, J. Am. Chem. Soc., 67, 566 (1945).

[55] Mattocks and Hartung, J. Am. Chem. Soc., 68, 2108 (1946).

[56] Chemische Fabrik vorm. Sandoz, Fr. pat. 844,225 [C. A., 34, 7296 (1940)]; Peyer, U. S. pat. 2,243,977 [C. A., 35, 5508 (1941)].

[57] Wenner, U. S. pat. 2,389,099 [C. A., 40, 1539 (1946)].

[58] Niemann and Redemann, J. Am. Chem. Soc., 68, 1932 (1946).
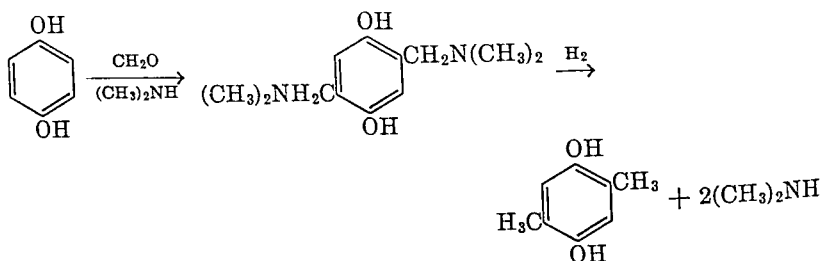
Quaternary Ammonium Compounds (Table XV). Little attention has been given to the hydrogenolysis of quaternary benzylammonium compounds. Tribenzylmethylammonium hydroxide reduced with palladium oxide furnishes toluene and benzylmethylamine.[51] Benzyl-phenyldimethylammonium chloride under similar conditions forms cyclohexyldimethylamine,[51] an unusual instance of the reduction of the benzene nucleus with a palladium catalyst.

Chemical hydrogenolysis of quaternary ammonium compounds has received more study, which chronologically preceded all the work on the catalytic methods. Emde,[3] by means of sodium amalgam, reduced cinnamyltrimethylammonium chloride to trimethylamine and propenyl-benzene. He found this to be a reaction characteristic for quaternary ammonium compounds containing the cinnamyl radical. The corre-

$$[C_6H_5CH{=}CHCH_2N(CH_3)_3]X \xrightarrow[Na \cdot Hg]{H_2}$$

$$C_6H_5CH{=}CHCH_3 + (CH_3)_3N + NaX$$
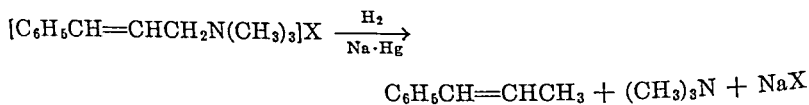
sponding saturated compounds, $[C_6H_5CH_2CH_2CH_2N(CH_3)_3]X$ and $[C_6H_5CHClCHOHCH_2N(CH_3)_3]X$, are stable under the same conditions. If the quaternary ammonium salt contains two cinnamyl groups, the products of the reaction are propenylbenzene and a cinnamyl-dialkylamine, which is stable until it is quaternized.

Benzyltrimethylammonium chloride furnishes toluene and trimethyl-amine,[3, 5] but allyltrimethylammonium chloride and hydroxide are not

$$[C_6H_5CH_2N(CH_3)_3]Cl \rightarrow C_6H_5CH_3 + (CH_3)_3N + NaCl$$
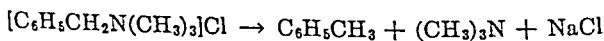
affected by sodium amalgam. Dibenzyldimethylammonium chloride forms toluene and benzyldimethylamine.[3, 5] Cinnamylbenzyldimethyl-ammonium chloride furnishes propenylbenzene and benzyldimethyl-amine, indicating that the cinnamyl-nitrogen bond is more easily cleaved under these conditions than is the benzyl-nitrogen bond.[6]

$$\left[C_6H_5CH{=}CHCH_2{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{N}}{-}CH_2C_6H_5 \right] Cl \rightarrow$$

$$C_6H_5CH{=}CHCH_3 + C_6H_5CH_2N(CH_3)_2 + NaCl$$
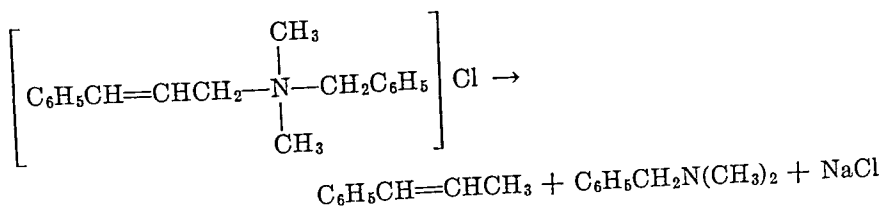
Hydrogenolytic cleavage of quaternary ammonium compounds has been used in the synthesis of methylpropylallylamine by the following sequence of reactions.[6]

$$(C_6H_5CH_2)_3N \xrightarrow{CH_3I} [(C_6H_5CH_2)_3NCH_3]I \xrightarrow[Na\cdot Hg]{H_2}$$

$$NaI + C_6H_5CH_3 + (C_6H_5CH_2)_2NCH_3 \xrightarrow{CH_2{=}CHCH_2I}$$

$$\left[(C_6H_5CH_2)_2N \overset{\displaystyle CH_3}{\underset{\displaystyle CH_2CH{=}CH_2}{\Big\langle}} \right] I \xrightarrow[Na\cdot Hg]{H_2}$$

$$NaI + C_6H_5CH_3 + C_6H_5CH_2N \overset{\displaystyle CH_3}{\underset{\displaystyle CH_2CH{=}CH_2}{\Big\langle}} \xrightarrow{CH_3CH_2CH_2I}$$

$$\left[C_6H_5CH_2{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_2CH_2CH_3}{|}}{N}}{-}CH_2CH{=}CH_2 \right] I \xrightarrow[Na\cdot Hg]{H_2}$$

$$\overset{\displaystyle CH_3CH_2CH_2}{\underset{\displaystyle CH_2{=}CHCH_2}{\Big\rangle}} NCH_3 + C_6H_5CH_3 + NaI$$
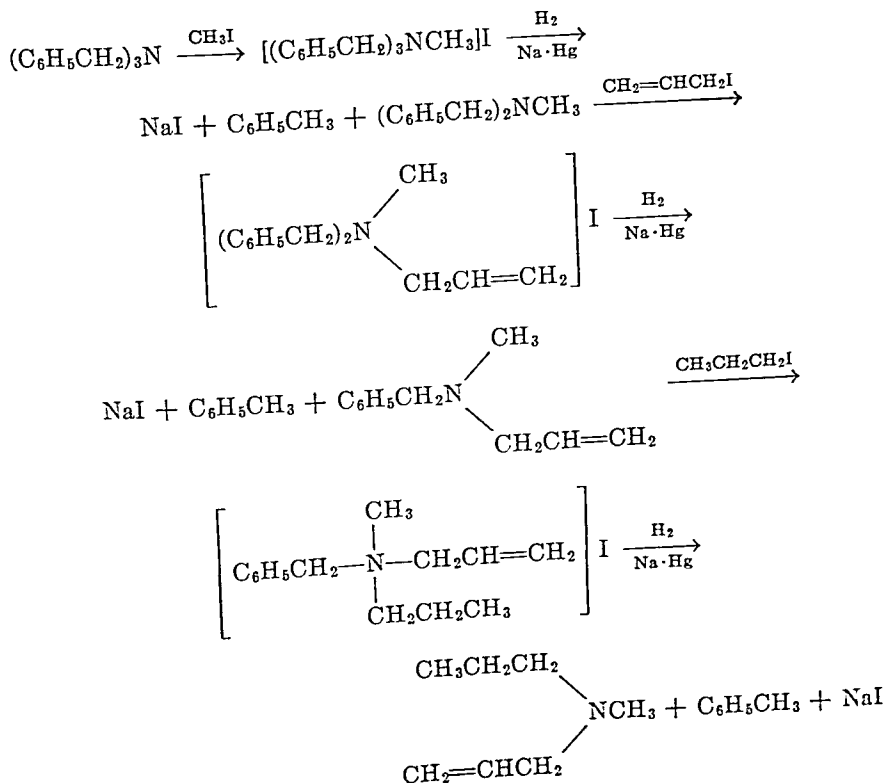
An analogous reaction takes place in the reductive degradation of *allo*-cryptopine methosulfate (XI, R = CH₃) to methyltetrahydrocryptopine (XII, R = CH₃),[8] and in the conversion of hunnemanine O-ethyl ether methosulfate (XI, R = C₂H₅) to tetrahydromethylhunnemanine O-ethyl ether (XII, R = C₂H₅).[62]

62 Manske, Marion, and Ledingham, *J. Am. Chem. Soc.*, **64**, 1659 (1942).

XI

allo-Cryptopine, R = CH₃

Hunnemanine O-ethyl ether, R = C₂H₅

XII
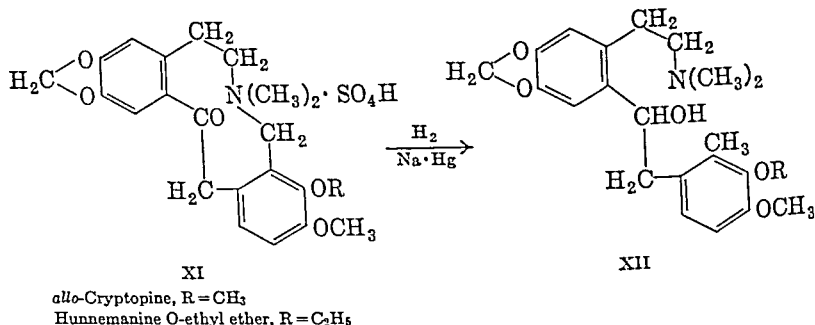
Simultaneous Cleavage of Benzyl-Oxygen and Benzyl-Nitrogen Bonds (Table XIV). The simultaneous removal of benzyl groups attached to oxygen and to nitrogen offers nothing new in principle. Examples of these reactions are shown in Table XIV.

Cleavage of Benzyl-Sulfur Bonds

Debenzylation of benzyl thio ethers presents special problems. The sulfhydryl group in the product is likely to poison the ordinary catalysts and, hence, the usual catalytic procedures are not applicable. So-called "sulfactive" catalysts are employed in hydrogenolytic reactions,[63, 64] but their use is not restricted to the removal of benzyl groups. Raney nickel as usually prepared contains appreciable amounts of hydrogen and will not only split thio ethers but will remove a sulfur atom, and such desulfurization is not limited to benzyl thio ethers.[65, 66] Catalytic procedures limited to the hydrogenolysis of benzyl-sulfur linkages have not been described.

Chemical methods, however, are available for S-debenzylation. They are extensions of the chemical methods used for removing the carbobenzyloxy group described on p. 275. Sodium in liquid ammonia reacts with carbobenzyloxycysteine to remove the carbobenzyloxy group and does not affect the sulfhydryl group. In these experiments the cysteine was not isolated but was oxidized to cystine, which was isolated in almost quantitative yield. When S-benzylcysteine was treated with sodium in liquid ammonia, debenzylation took place; the debenzylated product was oxidized, and cystine was isolated in a yield of 80%. The benzyl group appears not as toluene but as bibenzyl. Similar procedures

[63] Signaigo, U. S. pat. 2,402,686 [*C. A.*, **40**, 5766 (1946)].

[64] Farlow, Hunt, Langkammerer, Lazier, Peppel, and Signaigo, *J. Am. Chem. Soc.*, **70**, 1392 (1948).

[65] Bougault, Cattelain, and Chabrier, *Compt. rend.*, **208**, 657 (1939).

[66] Mozingo, Wolf, Harris, and Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

$$C_6H_5CH_2SCH_2CH(NH_2)CO_2H \xrightarrow[\text{Liquid NH}_3]{\text{Na}}$$

$$C_6H_5CH_2CH_2C_6H_5 + HSCH_2CH(NH_2)CO_2H$$

$$\downarrow O_2$$

$$\begin{matrix} SCH_2CH(NH_2)CO_2H \\ | \\ SCH_2CH(NH_2)CO_2H \end{matrix}$$
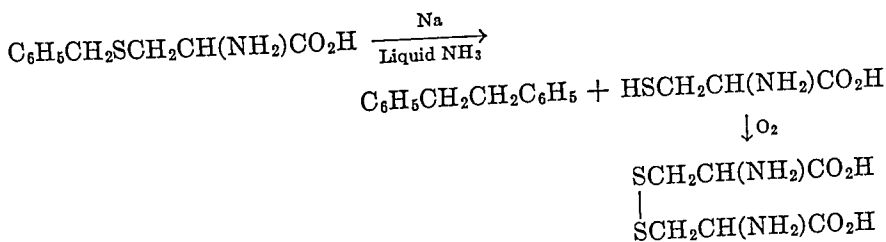
have been used for the preparation of homocystine,[67] dideuteromethionine and tetradeuterocystine,[68] and α-amino-β-mercaptobutyric acid.[69]

EXPERIMENTAL CONDITIONS AND CATALYSTS

Various palladium catalysts are described by Mozingo;[70] palladium black is prepared according to the directions of Tausz and Putnocky;[71] platinum black is described by Feulgen;[72] platinic oxide by Adams, Voorhees, and Shriner;[73] Raney nickel by Covert and Adkins.[74] Workers experienced with catalytic procedures need not be reminded that there are many modifications in the methods of preparing catalysts, especially those derived from the noble metals, and that there are still some imponderables in the process.

Catalytic reductions are usually carried out in the standard apparatus,[75] and in the absence of side reactions the course of hydrogenolysis parallels the drop in pressure of hydrogen. The choice of solvents is large. The effects of higher pressures have not been assayed, but generally it may be said that with palladium and platinum no high pressures are required and room temperature is usually adequate.

EXPERIMENTAL PROCEDURES

o-Tolylglucoside from Salicin.[18] In a microhydrogenation apparatus[76] is placed 0.25 g. of salicin in 25 ml. of water containing a trace of hydrochloric acid; 0.05 g. each of platinum black and palladium black are added. Absorption of hydrogen stops after one mole is taken up, in

[67] Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).
[68] Patterson and du Vigneaud, *J. Biol. Chem.*, **123**, 327 (1938).
[69] Carter, Stevens, and Ney, *J. Biol. Chem.*, **139**, 247 (1941).
[70] Mozingo, *Org. Syntheses*, **26**, 77 (1946).
[71] Tausz and Putnocky, *Ber.*, **52**, 1576 (1919).
[72] Feulgen, *Ber.*, **54**, 360 (1921).
[73] Adams, Voorhees, and Shriner, *Org. Syntheses Coll. Vol.*, I, 463 (1941).
[74] Covert and Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).
[75] Adams and Voorhees, *Org. Syntheses Coll. Vol.*, I, 61 (1941).
[76] Hyde and Scherp, *J. Am. Chem. Soc.*, **52**, 3359 (1930).

are then combined with the organic layer and dried; the solvent is removed at reduced pressure and the residue fractionated in vacuum; the p-dimethylaminotoluene distils at 77–79°/6.5 mm. and weighs 10.5 g. (78%).

p-**Aminodiphenylmethane from** p-**Aminobenzophenone.**[78] In a 2-l. Soxhlet flask is placed 136 ml. of 1.2 M lithium aluminum hydride in diethyl ether (7 equivalents per mole of ketone), diluted with 200 ml. each of benzene and dibutyl ether. The contents of the flask are heated to boiling (80°), and then a Soxhlet extraction apparatus is mounted on the flask, the thimble of the apparatus being charged with 13.8 g. (0.07 mole) of p-aminobenzophenone. Vigorous refluxing at 80° is maintained for one hour. The reaction mixture is cooled and carefully hydrolyzed with 200 ml. of 5% sodium hydroxide solution. The organic phase is separated, and the aqueous suspension is extracted with five 200-ml. portions of diethyl ether. The combined extracts, with the organic layer, are freed from solvents at reduced pressure. The residual viscous red oil is extracted repeatedly with hexane to yield 7.3 g. (57%) of a yellow oil which crystallizes on cooling with acetone and solid carbon dioxide. After drying, the p-aminodiphenylmethane melts at 34–35°.

The residue from the hexane extractions is a dark gum which, after crystallization from benzene, yields 2.1 g. (15%) of crude p-aminobenzhydrol, m.p. 108–112°; on repeated crystallization from water the product melts at 116–117°.

Dihydromorphine from Benzylmorphine.[11] Twenty-five grams of benzylmorphine hydrochloride is suspended in water and shaken in a hydrogen atmosphere with palladium-charcoal catalyst. Two moles of hydrogen is taken up. The catalyst is filtered, and from the filtrate are isolated toluene and dihydromorphine, the latter being recovered in quantitative yield by volatilizing the toluene and the water.

Toluene and Butanol from n-**Butyl Benzyl Ether.**[19] In a copper liner inside a steel bomb is placed 46 g. of n-butyl benzyl ether and 2.5 g. of Raney nickel. Hydrogenation is carried out at 175° and 150–200 atm. After one and one-half hours 93% of the ether has been converted to toluene and butanol.

5-Phenyl-1-pentanol from 2-Phenyltetrahydropyran.[23] Nine grams (0.056 mole) of 2-phenyltetrahydropyran is dissolved in 40 ml. of acetic acid solution containing 2.5% of 60% perchloric acid; 100 mg. of palladium-charcoal catalyst (5%) is added, and the mixture is reduced in the ordinary apparatus at 3 atm. Reduction is complete in thirty-five minutes. The catalyst is removed, the filtrate is poured into 10% sodium hydroxide solution, and 5-phenyl-1-pentanol is extracted with

ether or with tetrachloroethane and distilled, b.p. 142–148°/10 mm.; yield 72%.

(+,−)-Phenylalanylglycine from β-Phenyl-α-benzyloximinopropionylglycine.[39] Four grams (0.0123 mole) of β-phenyl-α-benzyloximinopropionylglycine is dissolved in a solution of 150 ml. of water and 2.5 ml. of concentrated ammonium hydroxide. The hydrogenation is carried out at 3 atm., using 3.5 g. of palladium catalyst (10%), and requires about two hours. The catalyst is then removed, and the filtrate is evaporated to dryness at reduced pressure and over a steam bath. The residue is triturated with methanol and washed with ether. The product, which is the dihydrate, weighs 2.4 g. (87%). It may be completely dried over phosphorus pentoxide to furnish (+,−)-phenylalanylglycine, m.p. 273–275° (dec).

3-Glyceraldehyde Phosphate from Benzylcycloacetalglyceraldehyde Phosphate.[79] In an apparatus which assures an atmosphere of pure hydrogen is placed 0.6 g. of palladium catalyst and 10 ml. of acetic acid which has been distilled from chromic acid. In a special bulb is placed 1.3 g. of pure benzylcycloacetalglyceraldehyde phosphate. The apparatus is shaken to saturate the catalyst; then the special bulb is inverted to add the substrate to the reaction mixture and shaking is resumed. Hydrogenolysis is complete in thirty to forty minutes at room temperature. The hydrogen in the apparatus is replaced by air, the mixture is removed and filtered, and the filtrate is concentrated at 30° at reduced pressure. The residue is washed on the centrifuge with one 4-ml. and with two 2-ml. portions of water; the undissolved substance is unchanged starting material. The combined aqueous washings are again concentrated at 30° to a syrup; final desiccation is achieved at 0.05 mm. The product is purified by washing on the centrifuge with methanol.

Barium D-Glucose-6-phosphate from 1,2-Isopropylidene-D-glucose.[50c] Dibenzyl chlorophosphonate, from 13.1 g. of dibenzyl phosphite, in 50 ml. of dry chloroform is added dropwise over a period of seventy-five minutes to a stirred solution of 11.0 g. of 1,2-isopropylidene-D-glucose in 100 ml. of pyridine at −10°. The mixture is allowed to warm to room temperature as stirring is continued and is then allowed to stand overnight. It is evaporated at reduced pressure, and the residual syrup is taken up in chloroform, washed with dilute sulfuric acid, then with water, and dried over anhydrous sodium sulfate; the solvent is evaporated. The residue is dissolved in ethanol, and the solution is heated to reflux for thirty minutes with 5 g. of Raney nickel to remove possible catalyst poisons. The solution is filtered and hydrogenated with a mixed catalyst, 0.5 g. of palladium oxide and 1.0 g. of palladium-charcoal

[79] Fischer and Baer, *Ber.*, 65, 337 (1932).

(10%), until no more hydrogen is taken up. The solution is filtered to remove catalyst. The isopropylidene group is removed by acid hydrolysis. D-Glucose-6-phosphate is isolated as the barium salt, $[\alpha]_D^{30}$ + 11.8°. The yield is 9 g. (42%).

2-Glycerol-β-D-glucoside from 1,3-Benzylideneglycerol-β-D-glucoside.[80] Benzylideneglycerol-β-D-glucoside, 1.25 g., is dissolved in 100 ml. of absolute ethanol and shaken with 0.9 g. of palladium black in an atmosphere of hydrogen. After an hour the hydrogen uptake ceases and glycerol-β-D-glucoside precipitates. It is filtered with the catalyst, from which it may be removed by dissolving in water. Evaporation of the aqueous solution leaves 0.9 g. (97%) of crystalline 2-glycerol-β-D-glucoside, m.p. 165°.

Phenylacetic Acid from Acetylmandelic Acid.[43] Two grams of acetylmandelic acid is dissolved in 10 g. of tetralin, and several grams of palladium-barium sulfate is suspended in the solution. The suspension is heated to 215°, the refluxing temperature of the solvent, and hydrogen is passed through for six hours, entering at the bottom of the boiling mixture. The mixture is then cooled and the catalyst removed. The phenylacetic acid is extracted with sodium carbonate solution, from which it is recovered by acidifying with hydrochloric or sulfuric acid. Crystallization from water yields the pure acid, m.p. 76° (60%).

L-Glutamylglycine Ethyl Ester from Carbobenzyloxy-L-glutamyl-glycine Ethyl Ester.[81] A solution of 8.2 g. of carbobenzyloxy-L-glutamyl-glycine ethyl ester in about 50 ml. of ethanol containing 2 ml. of glacial acetic acid is shaken with platinum black catalyst. After hydrogen absorption has ceased, the catalyst is removed and the solution evaporated; the residue is evaporated repeatedly with ethanol. The spongy mass which precipitates from ethanol on the addition of ether weighs 4.1 g. (80%). L-Glutamylglycine ethyl ester melts at 151°.

Diglycyl-L-cystine from Dicarbobenzyloxyglycyl-L-cystine.[82] To a stirred solution of 25 g. of dicarbobenzyloxyglycyl-L-cystine in 250 ml. of liquid ammonia are added small pieces of sodium until a blue color appears. The ammonia is then allowed to volatilize spontaneously, and the residual traces of ammonia are removed by evacuating the container for several hours on the water pump. The residue is taken up in cold water, and dilute sulfuric acid is added until the solution is acid to litmus. The glycylcysteine is precipitated with mercuric sulfate reagent, washed several times with water, and centrifuged. The complex is decomposed with hydrogen sulfide, and the precipitation with mercuric sulfate is

[80] Carter, *Ber.*, **63**, 1684 (1930).
[81] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, **111**, 225 (1935).
[82] Greenstein, *J. Biol. Chem.*, **128**, 241 (1939).

repeated. The final solution is made slightly alkaline with barium hydroxide solution, and the precipitated barium sulfate is removed by centrifuging. A few crystals of ferric oxide are added to the solution, and air is bubbled through it until the test with sodium nitroprusside shows the sulfhydryl group to be absent. The solution is heated with decolorizing charcoal, and the barium is precipitated quantitatively by the addition of sulfuric acid. The filtered solution is evaporated almost to dryness at reduced pressure. On addition of ethanol to the concentrate, the oxidized peptide, diglycylcystine, precipitates in gelatinous form. The mass is taken up in water and precipitated with ethanol, the process being repeated several times. After the last precipitation the mass is heated. It dissolves in the adhering ethanol and the peptide crystallizes from the hot solution in long prisms. The yield is 8.0 g. (57%), m.p. 232° (dec.), $[\alpha]_D^{24} - 108°$ for 75% solution in 0.1 N hydrochloric acid.

Di-n-hexylamine from Benzyldi-n-hexylamine.[60] A solution of 27.0 g. of benzyldi-n-hexylamine in 30 ml. of glacial acetic acid is shaken with 0.4 g. of platinic oxide in an atmosphere of hydrogen at 70°. After six hours the reduction is complete. The catalyst is removed, the filtrate is made strongly alkaline, and the di-n-hexylamine is extracted with diethyl ether. The extract is dried and fractionated; the amine distils at 110°/14 mm. The yield is practically quantitative.

Dialkylamines from Benzyldialkylamines.[52] The benzyldialkylamine, as free base or salt, is dissolved in twice its weight of glacial acetic acid, and platinum oxide catalyst, usually 1% of the weight of the amine, is added. Hydrogenation is carried out at 65–75° and 3 atm. Eight hours or less are required for reduction. The reaction mixture is diluted with methanol, the catalyst is removed by filtration, and excess hydrochloric acid is added to the filtrate which is concentrated at reduced pressure. To liberate any acetylated amine, the residue is digested on the steam bath with concentrated hydrochloric acid, 50 ml. for 0.1 mole amine, for several hours. Evaporation of the liquid leaves the amine hydrochloride, which may be purified by crystallization from an appropriate solvent; or the residue may be treated with alkali to liberate the free secondary amine, which may then be distilled.

2,3,5-Trimethylphenol from 2-Dimethylaminomethyl-3,5-dimethylphenol.[61] A solution of 18 g. of 2-dimethylaminomethyl-3,5-dimethylphenol in 200 ml. of dioxane is hydrogenated in the presence of 7.5 g. of copper chromium oxide for four hours at 165° and 177 atm. The catalyst is removed and the dioxane distilled. The residue, after acidification with a small amount of hydrochloric acid, is distilled with steam to

furnish 8 g. (58%) of 2,3,5-trimethylphenol. The product, crystallized from petroleum ether, melts at 93°.

1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol from α-Benzhydrylamino-3,4-dibenzyloxybutyrophenone.[14] To a solution of 28.9 g. (0.1 mole) of α-benzhydrylamino-3,4-dibenzyloxybutyrophenone hydrochloride in 150 ml. of absolute methanol, 0.5 g. of palladium sponge is added. The mixture is shaken with hydrogen at 55–70° and 3 atm. until 3 moles of hydrogen is taken up. The catalyst is removed, the toluene and the diphenylmethane are extracted with ether, and the aqueous layer is decolorized with charcoal and further hydrogenated with fresh catalyst until a fourth mole of hydrogen is taken up. The catalyst is again removed and the filtrate taken to dryness under reduced pressure. The residue is dissolved in absolute ethanol and again decolorized; then acetone and dry ether are added until precipitation is complete. The product weighs 14 g. (60%) and melts at 199–200° (dec.).

Benzylhydrazine from 1,1-Dibenzylhydrazine.[51] A solution of 4.1 g. of 1,1-dibenzylhydrazine in 50 ml. of absolute ethanol is hydrogenated with 400 mg. of palladium oxide. After hydrogen absorption ceases, the catalyst is removed and dry hydrogen chloride is led into the filtrate, whereupon 2.7 g. (88%) of benzylhydrazine hydrochloride precipitates. The product may be crystallized from ethanol.

Benzyldimethylammonium Chloride from Dibenzyldimethylammonium chloride.[3] Fifteen grams of dibenzyldimethylammonium chloride is dissolved in 50 ml. of water. Over a period of two days 50 g. of 5% sodium amalgam is added in small portions at room temperature. There is little evolution of gas, the solution becomes turbid, and after several hours an appreciable oily layer accumulates on the surface. On the second day the aqueous solution becomes clear, and the addition of more sodium now causes a vigorous evolution of gas. The liquid is decanted from mercury and extracted with ether; the aqueous layer contains a very small amount (about 0.1 g.) of the unchanged quaternary ammonium salt. From the ethereal extract the amine is removed with dilute hydrochloric acid. Concentration of the acidic extract leaves 9.0 g. of benzyldimethylammonium chloride (91%). Toluene may be recovered from the ether layer.

D-Homocystine from S-Benzyl-D-homocysteine.[83] A solution of 6.4 g. of S-benzyl-D-homocysteine in 40 ml. of liquid ammonia is treated with a slight excess of metallic sodium. The ammonia is allowed to evaporate spontaneously, and the residue is dissolved in 60 ml. of water. One-tenth gram of hydrated ferric chloride is added, and air is passed through the solution until the test with sodium nitroprusside for free sulfhydryl

83 du Vigneaud and Patterson, *J. Biol. Chem.*, **109**, 97 (1935).

groups is negative. The precipitated ferric hydroxide is removed by filtration, and the clear filtrate is made neutral to litmus with dilute hydrochloric acid. Pure D-homocystine precipitates; 2.85 g. (75%); after recrystallization from water the product melts at 281–284° (dec.).

α-Amino-β-mercapto-n-butyric Acid from α-Amino-β-benzylmercapto-n-butyric Acid.[69] Fifteen grams of α-amino-β-benzylmercapto-n-butyric acid is dissolved in 250 ml. of liquid ammonia and treated with small pieces of metallic sodium slightly more than two equivalents being necessary to produce a permanent blue color. Enough ammonium chloride is then added to discharge the color, plus 7 g. additional. The ammonia is allowed to evaporate, the final traces being removed at reduced pressure. To the residue are added 250 ml. of ether and 5 ml. of concentrated hydrochloric acid; the mixture is stirred and heated on the steam cone for several minutes. The ether is decanted, and the residue is again extracted with ether. The subsequent operations are carried out in an atmosphere of nitrogen. The residue is extracted with three 100-ml. portions of warm absolute ethanol containing a few drops of concentrated hydrochloric acid, and the combined extracts are taken to dryness under reduced pressure. The residue is dissolved in 80 ml. of absolute ethanol, and 800 ml. of anhydrous ether is added. The solution is cooled overnight, and the precipitate removed, washed with ether, and dried, yielding 9.8 g. of α-amino-β-mercapto-n-butyric acid hydrochloride. This is dissolved in 300 ml. of ethanol, and 3.8 ml. of concentrated ammonium hydroxide is added; on cooling, 6.4 g. (71%) of pure amino acid is obtained, m.p. 203–204° (dec.).

TABULAR SURVEY

In the seventeen tables that follow are listed examples of the reductive cleavage of benzyl groups. As indicated earlier, it is not possible to guarantee the completeness of the tables because many examples of the reaction are subordinated to other aspects of the articles in which they appeared. The survey of the literature was carried to July 1950.

TABLE I

BENZYL ALCOHOLS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5CH_2OH$	$C_6H_5CH_3$	Quant.	Pd-charcoal	Ethanol	25	3	Rapid	16
p-$CH_3OC_6H_4CH_2OH$	p-$CH_3OC_6H_4CH_3$	Quant.	Pd-charcoal	Ethanol	25	3	Rapid	16
p-$CH_3OC_6H_4CH_2OH$	p-$CH_3OC_6H_4CH_3$	85	Copper chromium oxide	Abs. CH_3OH	185	220–240	2.5 hr.	84
$3,4$-$(CH_2O_2)C_6H_3CH_2OH$	$3,4$-$(CH_2O_2)C_6H_3CH_3$	84	Copper chromium oxide	Dioxane	280	375	2 hr.	85
o-$H_2NC_6H_4CH_2OH$	o-$H_2NC_6H_4CH_3$	53	$LiAlH_4$	$(C_2H_5)_2O$	90	—	6 d.	32
$C_6H_{11}O_5$—O—$C_6H_4CH_2OH$ (salicin)	$C_6H_{11}O_5$—O—$C_6H_4CH_3$ (o-tolylglucoside)	—	Colloidal Pt	—	—	—	—	17
$C_6H_{11}O_5$—O—$C_6H_4CH_2OH$ (salicin)	$C_6H_{11}O_5$—O—$C_6H_4CH_3$ (o-tolylglucoside)	Quant.	Pt or Pd black	H_2O	25	1	20 min.	18

Note: References 84–165 are listed on pp. 325–326.

TABLE II

α-Substituted Benzyl Alcohols

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5CHOHC_6H_5$	$C_6H_5CH_2C_6H_5$	—	Pd-charcoal	Ethanol	25	3	Moderate	16
$C_6H_5CHOHCH_2OH$	$C_6H_5CH_2CH_2OH + C_6H_5CH_2CH_3$	Quant.	Pd-charcoal	Methanol	25	3	Moderate	16
$C_6H_5CHOHCH(CH_3)NHCH_3 \cdot HCl$	$C_6H_5CH_2CH(CH_3)NHCH_3 \cdot HCl$	60–80	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	80–90	1	10 min.	27
$C_6H_5CHOHCH(C_2H_5)NH_2$	$C_6H_5CH_2CH(C_2H_5)NH_2$	60–80	Pd-BaSO$_4$	$CH_3CO_2H + HBF_4$	80–90	1	0.5 hr.	27
$p\text{-}CH_3C_6H_4CHOHCH(C_2H_5)NH_2$	$p\text{-}CH_3C_6H_4CH_2CH(C_2H_5)NH_2$	60–80	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	80–90	1	—	27
$C_6H_5CHOHCH(C_2H_5)NHCH_3$	$C_6H_5CH_2CH(C_2H_5)NHCH_3$	80	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	80–90	1		27
$p\text{-}HOC_6H_4CHOHCH(C_2H_5)NH_2$	$p\text{-}HOC_6H_4CH_2CH(C_2H_5)NH_2$	60–80	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	80–90	1		27
$p\text{-}CH_3OC_6H_4CHOHCH(C_2H_5)NH_2$	$p\text{-}CH_3OC_6H_4CH_2CH(C_2H_5)NH_2$	60–80	Pd-charcoal	$CH_3CO_2H + HClO_4$	80–90	1		28
$C_6H_5CHOHCH_2NH_2$	$C_6H_5CH_2CH_2NH_2$	52	Pd-charcoal	Ethanol + HCl	25	1		16
$3,4\text{-}(CH_2O)_2C_6H_3CHOHCN$	$3,4\text{-}(CH_2O)_2C_6H_3CH_2CH_2NH_2$	81	Pd-charcoal	Ethanol + HCl	25	1	Moderate	16
$\beta\text{-}C_{10}H_7C(OH)(CH_3)CH_2CH_2CO_2Na$	$\beta\text{-}C_{10}H_7CH(CH_3)CH_2CH_2CO_2Na$	90	Copper chromium oxide	H_2O	160	147	2.5 hr.	86
$p\text{-}CH_3C_6H_4C(OH)(CH_3)CH_2CH_2CO_2Na$	$p\text{-}CH_3C_6H_4CH(CH_3)CH_2CH_2CO_2Na$	90	Copper chromium oxide	H_2O	200	170	2 hr.	87
$C_6H_5CHOHCO_2H$	$C_6H_5CH_2CO_2H$	90	Pd black	$CH_3CO_2H + H_2SO_4$	25	3.5	3.5 hr.	88
$C_6H_5CHOHCO_2H$	$C_6H_5CH_2CO_2H$	88	Pd black	$CH_3CO_2H + HClO_4$	25	2.5	9.5 hr.	88
$C_6H_5CHOHCO_2C_2H_5$	$C_6H_5CH_2CO_2C_2H_5$	75	Pd black	$CH_3CO_2H + H_2SO_4$	25	2.5	8 hr.	88

Compound	Yield (%)	Catalyst	Solvent	Temp.	Press.	Time	Ref.
$C_6H_5CHOHCO_2C_2H_5$	90	Pd black	$CH_3CO_2H + HClO_4$	25	2.5	8 hr.	88
$C_6H_5CH_2CO_2C_2H_5$	88	Pd black	CH_3CO_2H	100	2.5	1.5 hr.	88
$p\text{-}C_2H_5C_6H_4CHOHCO_2C_2H_5$	50	Pd black	$CH_3CO_2H + HClO_4$	25	2.5	—	88
$p\text{-}C_2H_5C_6H_4CHOHCO_2C_2H_5$	77	Pd black	$CH_3CO_2H + HClO_4$	60	2.5	1.5 hr.	88
$C_6H_5CH(OCOC_2H_5)CN$	92	Pd-charcoal	$CH_3OH + H_2SO_4$	25	2	6 min.	89
$C_6H_5CH(OCOC_2H_5)CN$	90	Pd-charcoal	$CH_3OH + HCl$	25	2	17 min.	89
$C_6H_5CH_2CN$	53	Pd-charcoal	CH_3OH	25	2	—	89
$C_6H_5CH_2CH_2NH_2$	75	Pd-charcoal	$CH_3CO_2H + H_2SO_4$	25	2	—	89
$C_6H_5CH_2CH_2NH_2$	70	Pd-charcoal	$CH_3CO_2H + HClO_4$	80	—	—	89
$C_6H_5CH_2CN$	90	Pd black	Benzene	—	—	—	89
$p\text{-}CH_3OC_6H_4CHOHCH_2CH_2CH_3$	60	Pd-charcoal	Abs. ethanol	25	4	2.5 hr.	23
$p\text{-}CH_3OC_6H_4CHOHCH_2CH(CH_3)_2$	60	Pd-charcoal	Abs. ethanol	25	4	2.5 hr.	23
$C_6H_5CHOHCHOHC_6H_5$	Quant.	Pd-charcoal	Abs. ethanol	25	4	2 hr.	23
$C_6H_5(CH_2)_4C_6H_5$	80	Pd-charcoal	Abs. ethanol	25	4	1.5 hr.	23
$C_6H_5CHOHCH(CH_3)C_6H_5$	75	Pd-charcoal	Abs. ethanol	25	4	1.5 hr.	23

Note: References 84–165 are listed on pp. 325–326.

Compound	Yield (%)	Catalyst	Solvent	Temp. (°C)		Rate/Time	Ref.
$m\text{-}CH_3OC_6H_4COC_2H_5$	—	Pd-charcoal	Ethanol	25	1	—	22
$m\text{-}HOC_6H_4CH_2C_2H_5$	Quant.	Pd-charcoal	Ethanol	25	1	45–90 min.	20
$p\text{-}HOC_6H_4COC_2H_5$	Quant.	Pd-charcoal	Ethanol	25	1	45–90 min.	20
$3,4\text{-}(HO)_2C_6H_3CH_2C_2H_5 + C_6H_5CHOHCH(CH_3)_2$	Quant.	Pd-charcoal	Ethanol	25	1	45–90 min.	20
$C_6H_5COCH(CH_2)_2$	—	Pd-charcoal	Ethanol	25	3	†	16
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH_3$	75	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH(CH_3)_2$	70	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH_2CH_3$	86	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH_2CH_2CH_3$	67–73	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH(CH_3)_2$	84	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH_2CH_2CH_2CH_3$	71	Pd-charcoal	Ethanol	25	1	—	90
$3,4\text{-}(HO)_2C_6H_3COCH_2CH_2CH_2CH_2CH_2CH_2CH_3$	71	Pd-charcoal	Ethanol	25	1	—	90
$C_6H_5CH_2CH_2CO\cdot C_2H_5$	85	Pd-BaSO$_4$	CH_3CO_2H	25	3	Moderate	27
$C_6H_5COC_6H_5$	Quant.	Pd-charcoal	CH_3OH	25	3	†	16
$C_6H_5COCH_2C_6H_5$	Quant.	Pd-charcoal	CH_3OH	25	3	—	16
$(C_6H_5)_2CHCOC_6H_5$	Quant.	Pd-charcoal	Ethanol	25	3	Moderate	16
$p\text{-}C_6H_5C_6H_4COC_6H_5$	Quant.	Pd-charcoal	Ethanol + ethyl acetate	—	3	Slow	16
$\alpha\text{-}C_{10}H_7COC_6H_5$	95	Pd-charcoal	Ethanol	25	3	Moderate	16
Fluorenone	Quant.	Pd-charcoal	Ethanol	25	3	Moderate	16
$p\text{-}CH_3OC_6H_4COCHOHC_6H_4OCH_3\text{-}p$	Quant.	Pd-charcoal	Ethanol + ethyl acetate	25	3	Moderate	16
$3,4\text{-}(CH_2O_2)C_6H_3CH_2CH_2CH_2C_6H_3(O_2CH_2)\text{-}3,4$	—	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	†	27
$C_6H_5COCH(C_3H_7\text{-}n)NHCH_3$	67	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	3 hr.	27
$C_6H_5COC(C_2H_5)=NOH$	56	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	—	27
$C_6H_5COC(C_3H_7\text{-}n)=NOH$	60	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	—	27
$p\text{-}CH_3C_6H_4COC(C_2H_5)=NOH$	56	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	—	27
$p\text{-}CH_3OC_6H_4CH_2CH(C_2H_5)NH_2$	77	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	—	27
$p\text{-}HOC_6H_4CH_2CH(C_2H_5)NH_2$	35	Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$	—	—	—	27
$\alpha\text{-}C_{10}H_7CH_2CH(CH_3)NH_2$		Pd-BaSO$_4$	$CH_3CO_2H + HClO_4$				27

Note: References 84–165 are listed on pp. 325–326.

* Reduction to the carbinol was rapid; reduction of the carbinol was slow.

† Reduction to the carbinol was rapid; reduction of the carbinol was slow and incomplete.

‡ The reduction was rapid until half completed, then slow.

TABLE IV—*Continued*

KETONES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
(structure: H–C–OH, H–C–C=NOH, C=O on benzene ring)	(structure: H–C–, C–NH₂ on benzene ring)	90	Pd-BaSO₄	CH₃CO₂H + HClO₄	—	—	—	27
$COCH_2CH_2CO_2Na$ (with CH₂ fused ring structure)	$CH_2CH_2CH_2CO_2Na$ (with CH₂ fused ring structure)	66	Copper chromium oxide	NaOH + H₂O	200	—	5-10 hr.	91
$\alpha\text{-}C_{10}H_7COCH(CH_3)CH(CH_3)CO_2Na$	$\alpha\text{-}C_{10}H_7CH_2CH(CH_3)CH(CH_3)CO_2Na$	81	Copper chromium oxide	H₂O	140	130	5-10 hr.	92
(polycyclic structure with =O and CH₂)	(polycyclic structure with CH₂)	90	Copper chromium oxide	Abs. ethanol	160	—	1 hr.	91
$C_6H_5COCH=CHC_6H_5$	$C_6H_5(CH_2)_3C_6H_5$	Quant.	Pd-charcoal	Abs. ethanol	25	4	1 hr.	93
$p\text{-}CH_3C_6H_4COCH=CHC_6H_5$	$p\text{-}CH_3C_6H_4(CH_2)_3C_6H_5$	Quant.	Pd-charcoal	Abs. ethanol	25	4	1 hr.	93
$C_6H_5COCH=CHC_6H_4OCH_3\text{-}p$	$C_6H_5(CH_2)_3C_6H_4OCH_3\text{-}p$	Quant.	Pd-charcoal	Abs. ethanol	25	4	1 hr.	93

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5COCH{=}CHC_6H_3(O_2CH_2)\text{-}3,4$		60	Pd-charcoal	Abs. ethanol	25	4	1 hr.	23
$C_6H_5COCH{=}CHC_6H_5$		80	Pd-charcoal	Abs. ethanol	25	4	1.5 hr.	23
$p\text{-}CH_3OC_6H_4COCN$		78	Pd black	$CH_3CO_2H + H_2SO_4$	60	3.5	3.5 hr.	93
$3,4\text{-}(CH_3O)_2C_6H_3COCN$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH_2$	72	Pd black	$CH_3CO_2H + H_2SO_4$	60	3.5	3 hr.	93
$p\text{-}CH_3C_6H_4COCH_2CH_2CO_2H$	$p\text{-}CH_3C_6H_4(CH_2)_3CO_2H$	79	Pd-charcoal	CH_3CO_2H	65	2.6	25 min.	94
$p\text{-}CH_3OC_6H_4(CH_2)_3CO_2H$	$p\text{-}CH_3OC_6H_4(CH_2)_3CO_2H$	75	Pd-charcoal	CH_3CO_2H	65	2.0	40 min.	91
$o\text{-}C_6H_5COC_6H_4CO_2H$	$o\text{-}C_6H_5CH_2C_6H_4CO_2H$	95	Pd-charcoal	CH_3CO_2H	65	2.6	1.25 hr.	94
$C_6H_5CHOHCOC_6H_5$	$C_6H_5CH_2CH_2C_6H_5$	74	Pd-charcoal	CH_3CO_2H	65	2.6	8 hr.	95
[ring structure, CH_3COO]	[ring structure, CH_3COO]	94	Pd-charcoal	CH_3CO_2H	65	—	—	95
$C_6H_5COCH_3$	$C_6H_5C_2H_5$	—	Pd Black-S	CH_3OH	25	2.5	1 hr.	21
$p\text{-}H_2NC_6H_4COC_6H_5$	$p\text{-}H_2NC_6H_4CH_2C_6H_5$	57	$LiAlH_4$	$(C_2H_5)_2O$	80	—	1 hr.	32
$p\text{-}H_2NC_6H_4COC_6H_4NH_2\text{-}p$	$p\text{-}H_2NC_6H_4CH_2C_6H_4NH_2\text{-}p$	32	$LiAlH_4$	$(C_2H_5)_2O$	60	—	3 d.	32
$p\text{-}CH_3OC_6H_4COC_6H_4OCH_3\text{-}p$	$p\text{-}CH_3OC_6H_4CH_2C_6H_4OCH_3\text{-}p$	46	$LiAlH_4$	$(C_2H_5)_2O$	90	—	11 d.	32

Note: References 84–165 are listed on pp. 325–326.
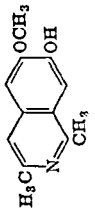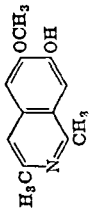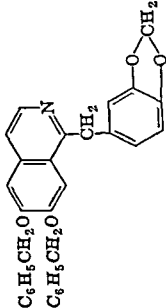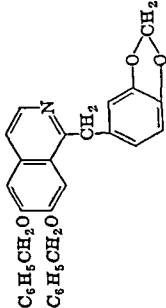
TABLE V

BENZYL ETHERS
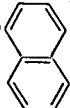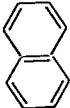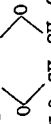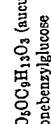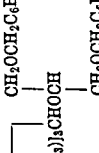
Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5CH_2OCH_3$	CH_3OH	64	Raney Ni	—	160	150–250	30 min.	19
$C_6H_5CH_2OC_2H_5$	$C_6H_5CH_3 + C_2H_5OH$	—	H_2PtCl_6	—	—	—	—	7
$C_6H_5CH_2O(CH_2)_3CH_3$	$n\text{-}C_4H_9OH$	92	Raney Ni	None	175	150–250	1.5 hr.	19
$C_2H_5CH_2OCH(CH_3)C_2H_5$	$C_2H_5CH(CH_3)OH$	80	Raney Ni	—	125	150–250	30 min.	19
$C_6H_5CH_2O(CH_2)_4CH_3$	$CH_3CH_2CH_2CH_2CH_2OH$	Quant.	Pd-charcoal	Ethanol	25	—	—	12
$C_6H_5CH_2OC_{12}H_{25}\text{-}n$	$n\text{-}C_{12}H_{25}OH$	72	Raney Ni	—	100	150–250	1.5 hr.	19
$C_6H_5CH_2O(CH_2)_3C_6H_5$	$C_6H_5(CH_2)_3OH$	71	Raney Ni	—	100	150–200	30 min.	19
$C_6H_5CH_2O(CH_2)_3OH$	$HO(CH_2)_3OH$	13	Raney Ni	—	175	150–250	7 hr.	19

Note: References 84–165 are listed on pp. 325–326.

TABLE V—Continued

BENZYL ETHERS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
C6H5CH2OCH2CH2OC2H5	C2H5OCH2CH2OH	64	Raney Ni	—	175	150–250	4 hr.	19
C6H5CH2OCH2CH2OC6H5	C6H5OCH2CH2OH + C6H11OH	37	Raney Ni	—	150	150–250	1.3 hr.	19
2,3-(CH3O)2C6H3CH=CH(CH2)2OCH2C6H5	2,3-(CH3O)2C6H3(CH2)3OH	97	Pd black	CH3CO2H	25	2–3	5 hr.	36
C6H5CH2OC6H5	C6H11OH	Quant.	Pd-charcoal	CH3CO2H	25	1	—	11
C6H5CH2OC6H5	C6H5OC6H11	Quant.	Raney Ni	—	100	150–250	24 min.	19
o-CH3OC6H4OCH2C6H5	o-CH3OC6H4OH	Quant.	Pd-charcoal	—	25	1	—	11
o-CH3C6H4OCH2C6H5	o-CH3C6H4OH	85	Raney Ni	—	125	150–250	1 hr.	19
m-CH3C6H4OCH2C6H5	m-CH3C6H4OH + m-CH3C6H10OH	74	Raney Ni	—	150	150–250	60 min.	19
p-CH3C6H4OCH2C6H5	p-CH3C6H4OH + p-CH3C6H10OH	86	Raney Ni	—	150	150–250	1 hr.	19
o-CH3O2CC6H4OCH2C6H5	o-CH3O2CC6H4OH	77	Raney Ni	—	150	150–250	24 min.	19
C6H5CH2OC6H11O5	C6H12O6 (glucose)	—	Pd	—	25	1	—	18
C6H5CH2OC6H11O5	C6H12O6 (glucose) + C5H11O5OCH2C6H11 *	—	Pt	—	25	1	—	18
C6H5CH2OC6H11O5	C6H12O6 (glucose)	75	Pt black	Dil. HCl	25	1	90 min.	18
C6H5CH2OC6H11O5	C6H12O6 (glucose)	99	Pd black	H2O	25	1	3 hr.	18
[naphthalene/isoquinoline structure: H3C, N, OCH2C6H5, OCH2C6H5, CH3]	[isoquinoline structure: H3C, N, CH3, OCH3, OH]	80	Pd-charcoal	Ethanol + toluene	25	1	—	34
[isoquinoline structure with C6H5CH2O, C6H5CH2O, N, CH2, methylenedioxyphenyl (O–CH2–O)]	[isoquinoline structure with N, CH2, OCH3, OH, methylenedioxyphenyl (O–CH2–O)]	—	—	—	—	—	—	35
C6H5CH2OC17H18O2N(benzylmorphine)	C17H21O3N(dihydromorphine)	Quant.	Pd-charcoal	H2O	25	1	—	11
p-C6H5CH2OC6H4COCH2N(CH3)COC6H5	p-HOC6H4COCH2N(CH3)COC6H5	—	Pd	—	—	—	—	96

Compound	Product	Yield	Catalyst	Solvent	Temp. (°)	Pressure	Time	Reference
(naphthalene) –CHOHCH₂N(C₃H₇-n)₂, –OCH₂C₆H₅	Dihydronaphthalene derivative; no debenzylation	—	PtO₂	—	—	—	—	97
(naphthalene) –CHOHCH₂N(C₄H₉-n)₂, –OCH₂C₆H₅	Dihydronaphthalene derivative; no debenzylation	—	PtO₂	—	25	2.5	—	97
3-CH₃O-4-HOC₆H₃CHOHCH(NH₂)CH₃		96	Pd-charcoal	Abs. CH₃OH	25	1	10 min.	34
3,4-(HO)₂C₆H₃CHOHCH(NH₂)CH₃		Quant.	Pd-charcoal	Abs. CH₃OH-HCl	25	1	3 min.	98
3-CH₃O-4-CH₃CH₂OC₆H₃CHOHCH(NH₂)CH₃; 3,4-(CH₃CH₂O)₂C₆H₃CHOHCH(NH₂)CH₃		—	Pd	70% CH₃CO₂H	25	1	—	79
BaO₃POH₂C—CH—CH—CH—CH₂OC₆H₅ / O / C₆H₅OCH₂O—CH—CH—CH—CH₂OPO₃Ba	CHO, 2CHOH, CH₂OPO₃H₂	—						
CH₃OH₂C—CH—CH—CH—OCH₂C₆H₅ / O / C₆H₅OCH₂O—CH—CH—CH₂OCH₃	CH₂OCH₃, 2CHOH, CHO	65	Pd	CH₃CO₂H	25	1	9 min.	99
C₆H₁₁O₅OC₉H₁₃O₃ (aucubin)	C₆H₁₂O₆ + C₉H₁₈O₂ (tetrahydrodesoxyaucubigenin)	—	Colloidal Pt	—	—	—	—	17
Diacetonebenzylglucose	Diacetoneglucose	Good	Na + ethanol	Ethanol	—	—	—	100
Diacetonebenzylglucose	Monoacetoneglucose	—	Pt	CH₃CO₂H †	—	—	—	100
CH₃CO₂CH₂CH₂CH[CH(OCOCH₃)]₃CHOCH, CH₂OCH₂C₆H₅ … CH₂OCH₂C₆H₅	CH₂OH ‡	Quant.	Pt	Ethanol	25	1	—	80
p-CH₃OC₆H₄CH₂OCH₂OCH₂C₆H₅	p-CH₃OC₆H₄CH₃	Quant.	Pd-charcoal	Ethanol	25	3	Rapid	16
C₆H₅CH₂OCH₂C₁₀H₇-β	Hydrogenated β-naphthola	60	Raney Ni	—	125	150–250	30 min.	19
(C₆H₅)₃COCH₂(CHOCOCH₃)₄CH₂OC(C₆H₅)₃	CH₂OH(CHOCOCH₃)₄CH₂OH	60	Pt black	CH₃CO₂H	40–50	—	20 hr.	15

Note: References 84–165 are listed on pp. 325–326.

* Hydrogenolysis and hydrogenation of the aromatic nucleus are competing reactions. Hydrogenation may follow hydrogenolysis, but not vice versa.

† In ethanol no cleavage occurred, and more highly hydrogenated products were formed.

‡ When this product was hydrogenated in ethanol for one hour with Pd black, β-glyceroglucoside was formed.

TABLE V—*Continued*
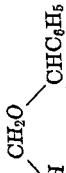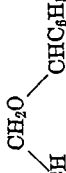
BENZYL ETHERS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
CH₃OH(CHOCOCH₃)₂CHCH₂OC(C₆H₅)₃ $\overbrace{}^{O}$	CH₃OCH(CHOCOCH₃)₂CHCH₂OH $\overbrace{}^{O}$	—	Pt black	CH₃CO₂H	40–50	—	32 hr.	15
CH₂OC(C₆H₅)₃ CHOCOC₁₇H₃₅ CH₂OCOC₁₇H₃₅	CH₂OH CHOCOC₁₇H₃₅ CH₂OCOC₁₇H₃₅	92	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101
CH₂OC(C₆H₅)₃ CHOCOC₆H₅ CH₂OCOC₆H₅	CH₂OH CHOCOC₆H₅ CH₂OCOC₆H₅	83	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101
CH₂OC(C₆H₅)₃ CHOCOC₁₆H₃₁ CH₂OCOC₁₇H₃₅	OH₂OH CHOCOC₁₆H₃₁ CH₂OCOC₁₇H₃₅	91	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101
CH₂OC(C₆H₅)₃ CHOCOC₁₇H₃₅ CH₂OCOC₁₆H₃₁	CH₂OH CHOCOC₁₇H₃₅ CH₂OCOC₁₆H₃₁	93	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101
CH₂OC(C₆H₅)₃ CHOCOC₆H₅ CH₂OCOC₁₇H₃₅	CH₂OH CHOCOC₆H₅ CH₂OCOC₁₇H₃₅	87	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101
CH₂OC(C₆H₅)₃ CHOCOC₁₇H₃₅ CH₂OCOC₆H₅	CH₂OH CHOCOC₁₇H₃₅ CH₂OCOC₆H₅	83	Pd-charcoal	Abs. ethanol	40–50	—	2–3 hr.	101

TABLE V—*Continued*

BENZYL ETHERS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
(structure: OCH₃, C₂H₅CH₂O-benzofuran-CO₂C₂H₅)	(structure: OCH₃, HO-benzofuran-CO₂C₂H₅)	Quant.	Pd-charcoal	CH₃CO₂H	—	1	15 min.	111
(structure: OCH₃, C₆H₅CH₂O-dihydrobenzofuran)	(structure: OCH₃, HO-dihydrobenzofuran)	—	Pd-charcoal	CH₃CO₂H	—	1	20 min.	111
(structure: OCH₃, C₆H₅CH₂O-dihydrobenzofuran)	(structure: OCH₃, HO-dihydrobenzofuran)	Quant.	Pd-charcoal	CH₃OH	—	—	—	112
(isoquinoline structure: CH₃, N, OC₂H₅, OCH₃, CH₃O, CH₃O)	(isoquinoline structure: CH₃, N, OH, OCH₃, CH₃O, CH₃O)	96	Pd-charcoal	Abs. ethanol	—	—	—	113
(cyclic structure: CHC₆H₅, CH₂, O, H₂C, H₂C, C, H₂)	$C_6H_5(CH_2)_3OH$	72	Pd-charcoal	CH₃CO₂H + HClO₄	—	3	35 min.	33

TABLE VI

ACETALS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5C(OC_2H_5)_2CHOHC_6H_5$	$C_6H_5CH_2CH_2C_6H_5$	—	Pd-charcoal	CH_3CO_2H + $HClO_4$	—	1	30 min.	33
$C_6H_5CH(OC_2H_5)_2$	$2C_2H_5OH$	—	Pd black	CH_3CO_2H	—	—	—	10
$C_6H_5CH(OC_2H_5)_2$	$C_6H_{11}CH_3$ + $C_6H_{11}CH_2OH$ + $C_6H_{11}CH_2OC_2H_5$	—	Pt black	CH_3CO_2H	25	—	—	40
$p\text{-}CH_3C_6H_4CH(OC_2H_5)_2$	$p\text{-}CH_3C_6H_4CH_3$ + $2C_2H_5OH$	—	Pd black	CH_3CO_2H	—	—	—	10
$p\text{-}CH_3OC_6H_4CH(OC_2H_5)_2$	$p\text{-}CH_3OC_6H_4CH_3$ + $2C_2H_5OH$	—	Pd black	CH_3CO_2H	—	—	—	10
$C_6H_5CO_2CH\overset{\displaystyle CH_2O}{\underset{\displaystyle CH_2O}{\big\langle}}CHC_6H_5$	$C_6H_5CO_2CH(CH_2OH)_2$	98	Pd	Abs. ethanol	25	1	1–2 hr.	41
$CH_3CO_2CH\overset{\displaystyle CH_2O}{\underset{\displaystyle CH_2O}{\big\langle}}CHC_6H_5$	$CH_3CO_2CH(CH_2OH)_2$	—	Pd	Abs. ethanol	25	1	—	41
$C_{15}H_{31}CO_2CH\overset{\displaystyle CH_2O}{\underset{\displaystyle CH_2O}{\big\langle}}CHC_6H_5$	$C_{15}H_{31}CO_2CH(CH_2OH)_2$	96	Pd black	Abs. ethanol	25	1	90 min.	41
Benzal-α-methylglucoside	α-Methylglucoside	—	Pt sponge	Ethanol	25	1	—	42
$C_6H_5CH(OCOCH_3)_2$	$C_6H_5CH_3$	—		—	25	1	—	7

Note: References 84–165 are listed on pp. 325–326.

TABLE VII

BENZYL ESTERS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
$C_6H_5CH_2OCOCH_3$	$C_6H_5CH_3$	—	Pd	CH_3CO_2H	25	1	—	7
$C_6H_5CH_2OCOC_6H_5$	$C_6H_5CH_3 + C_6H_5CO_2H$	94	Pd	Xylene	140	1	—	9
$C_6H_5CH(CO_2H)OCOCH_3$	$C_6H_5CH_2CO_2H$	20–60 †	Pd-BaSO$_4$	Xylene	150–215	1	4–6 hr.	43
$p\text{-}CH_3OC_6H_4CH(CO_2H)OCOCH_3$	$p\text{-}CH_3OC_6H_4CH_2CO_2H$	40	Pd-BaSO$_4$	—	—	1	—	43
$o\text{-}ClC_6H_4CH(CO_2H)OCOCH_3$	$o\text{-}ClC_6H_4CH_2CO_2H$	—	Pd-BaSO$_4$	Tetralin	215	1	—	43
$o\text{-}CH_3OC_6H_4CH(CO_2H)OCOCH_3$	$o\text{-}CH_3OC_6H_4CH_2CO_2H$	66	Pd-BaSO$_4$	—	—	1	—	43
$C_6H_5CH(CN)COCH_3$	$C_6H_5CH_2CH_2NH_2$	74	Pd-charcoal	Ethanol + HCl	25	1	75 min.	28
$C_6H_5CH_2OCOCH_2NHCONHCOCH_2Cl$	$ClCH_2CONHCONHCH_2CO_2H$	65	Pd	Dil. CH_3OH	100	1	4 hr.	117
Penicillin benzhydryl ester	Penicillin	—	Colloidal Pd	—	—		—	118
$(CH_3)_2C(SO_3H)CH(NH_2)CO_2CH_2C_6H_5$	$(CH_3)_2C(SO_3H)CH(NH_2)CO_2H$	—	Pd	H_2O	—		—	119
$p\text{-}CH_3OC_6H_4CO_2CH(C_6H_5)_2$	$p\text{-}CH_3OC_6H_4CO_2H$	Quant.	Pd-charcoal	Abs. ethanol	25		25 min.	120
$C_6H_5CH_2CO_2CH(C_6H_5)_2$	$C_6H_5CH_2CO_2H$	Quant.	Pd-charcoal	Abs. ethanol	25		25 min.	120
$o\text{-}CH_3CO_2C_6H_4CO_2CH(C_6H_5)_2$	$o\text{-}CH_3CO_2C_6H_4CO_2H$	Quant.	Pd-charcoal	Abs. ethanol	25		25 min.	120
$C_6H_5CH=CHCO_2CH(C_6H_5)_2$	$C_6H_5CH_2CH_2CO_2H$	Quant.	Pd-charcoal	Abs. ethanol	25		1 hr.	120
$CH_3CO_2CH_2(CHOCOCH_3)_4CO_2CH(C_6H_5)_2$	$CH_3CO_2CH_2(CHOCOCH_3)_4CO_2H$	82	Pd-charcoal	Abs. ethanol + ethyl acetate	25		—	120
$C_{23}H_{36}(OH)CO_2CH(C_6H_5)_2$ (hydroxycholenic acid)	$C_{23}H_{36}(OH)CO_2H$ (hydroxycholenic acid)	97	Pd-charcoal	Abs. ethanol	25		45 min.	120
$C_{23}H_{36}(OH)_3CO_2CH(C_6H_5)_2$	$C_{23}H_{36}(OH)_3CO_2H$ (cholic acid)	Quant.	Pd-charcoal	Abs. ethanol	25		24 hr.	120
$C_{23}H_{36}(OCOCH_3)_3CO_2CH(C_6H_5)_2$	$C_{23}H_{36}(OCOCH_3)_3CO_2H$ (triacetylcholic acid)	Quant.	Pd-charcoal	Abs. ethanol	25		4 d.	120
$C_{28}H_{45}CHOHCO_2CH(C_6H_5)_2$	$C_{28}H_{45}CHOHCO_2H$ (oleanolic acid)	—	Pd-charcoal	Abs. ethanol	25		7 d.	120
$C_{28}H_{44}O(CO_2CH(C_6H_5)_2)_2$	$C_{28}H_{44}(CO_2H)_2$ (quinovic acid)	—	Pd-charcoal	Abs. ethanol	25	60	3 hr.	120
$n\text{-}C_7H_{15}COC(C_8H_{17}\text{-}n)(CO_2CH_2C_6H_5)_2$	$n\text{-}C_7H_{15}COC_9H_{19}\text{-}n$	91	Pd-charcoal	Ethanol + ethyl acetate	25		—	44, 121

Note: References 81–165 are listed on pp. 325–326.

* Under the same conditions benzaldehyde was reduced via benzyl alcohol to dibenzyl ether.

† The yield is a function of time and temperature.

TABLE VII—Continued

Benzyl Esters

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
$n\text{-}C_{10}H_{21}COCCH_2CH(CH_2)_3(CO_2CH_2C_6H_5)_2$	$n\text{-}C_{10}H_{21}COCH_2CH_2CH(CH_2)_2$	80	Pd-charcoal	Ethanol	25	—	—	44, 121
$COC(C_8H_{17}\text{-}n)(CO_2CH_2C_6H_5)_2$	$n\text{-}C_8H_{10}CO(CH_2)_3COC_6H_{17}\text{-}n$	78	Pd-charcoal	Ethanol + ethyl acetate	25	—	—	44, 121
$(CH_2)_6\big[\;COC(C_8H_{17}\text{-}n)(CO_2CH_2C_6H_5)_2$	$n\text{-}C_{10}H_{21}COCH_2CH_2CO_2H$	66	Pd-charcoal	Ethanol	25	—	—	44, 121
$n\text{-}C_{10}H_{21}COC(CO_2CH_2C_6H_5)_2\,CH_2CO_2CH_2C_6H_5$	$C_2H_5OCO(CH_2)_3COC_8H_{17}\text{-}n$	81	Pd-charcoal	Ethanol	25	—	—	121
$C_2H_5OCO(CH_2)_3COC(C_7H_{15}\text{-}n)(CO_2CH_2C_6H_5)_2$	$n\text{-}C_4H_9CH(C_2H_5)CO(CH_2)_{10}CO_2H$	78	Pd-charcoal	Ethanol + ethyl acetate	25	—	—	44
$n\text{-}C_4H_9CH(C_2H_5)COC(C_{10}H_{20}CO_2CH_2C_6H_5)(CO_2CH_2C_6H_5)_2$	$HO(CH_2)_{10}COC_9H_{17}\text{-}n$	60	Pd-charcoal	Ethanol + ethyl acetate	25	—	—	44
$CH_3CO_2(CH_2)_{10}COC(C_9H_{17}\text{-}n)(CO_2CH_2C_6H_5)_2$	$C_6H_5CHOHCOC_{13}H_{27}\text{-}n$	65	Pd-charcoal	Ethanol + ethyl acetate	25	—	—	44
$C_6H_5CHOHCOC(C_{11}H_{23}\text{-}n)(CO_2CH_2C_6H_5)_2$	$m\text{-}CH_3OC_6H_4COCH_2CH_2CO_2H$	83	Pd-charcoal	Ethanol + ethyl acetate	25	—	—	44
$C_6H_5CH(OCOCH_3)COC(C_{11}H_{23}\text{-}n)(CO_2CH_2C_6H_5)_2$								
$m\text{-}CH_3OC_6H_4COC(CO_2CH_2C_6H_5)_2CH_2CO_2CH_2C_6H_5$	$C_2H_5O(PO)(OH)_2$	50	Pd-charcoal	Ethanol	—	1	—	122
$(C_6H_5CH_2O)_2PO(OC_2H_5)$	$(CH_3)_2CHCH_2CH_2O(PO)(OH)(OCH_2C_6H_5)$	—	Pd-charcoal	CH_3OH	—	1	—	122
$(C_6H_5CH_2O)_2PO[OCH_2CH_2CH(CH_3)_2]$	$\beta\text{-}C_{10}H_7O(PO)(OH)_2$	80	Pd-charcoal	CH_3OH	—	1	—	122
$\beta\text{-}C_{10}H_7O(PO)(OCH_2C_6H_5)_2$	$C_2H_5O(PO)(OH)_2$	51	PdO	Ethanol	—	1	10 min.	123
$C_2H_5O(PO)(OCH_2C_6H_5)_2$	$C_2H_5O(PO)(OH)_2$	—	Pd-charcoal	$CH_3OH + H_2O$	—	1	—	124
$C_2H_5O(PO)(OCH_2C_6H_5)_2$								

	Catalyst	Solvent				Ref.
	—	Ethanol + $C_6H_{11}N(CH_3)_2$	—	—	—	124
	Pd-charcoal	$CH_3OH + H_2O$	—	—	—	124
	Pd-charcoal	Ethanol	—	—	—	124
	Pd-charcoal	Ethanol	—	—	—	121
	Pd-charcoal	Ethanol	—	—	—	124
	Raney Ni	Ethanol	130	—	—	121

Structures (left → right products):

$C(CH_3)_2$ bridged: HCO—HCO—HOCH—HCOH—HC—
$CH_2O(PO)(OCH_2C_6H_5)_2$ / $CH_2O(PO)(OH)_2$

$C_6H_5O(PO)(OCH_2C_6H_5)_2$ / $C_6H_5O(PO)(OH)_2$

$3,4\text{-}(CH_2)_2C_6H_3NHCH_2(CHOH)_3CH_2O(PO)(OCH_2C_6H_5)_2$ / $3,4\text{-}(CH_2)_2C_6H_3NHCH_2(CHOH)_3\text{-}CH_2O(PO)(OH)_2$

Naphthalene with CH_3: $O(PO)(OCH_2C_6H_5)_2$ / $O(PO)(OCH_2C_6H_5)_2$; $O(PO)(OH)_2$ / $O(PO)(OH)_2$

$(C_6H_5CH_2O)_2(PO)OC_6H_4CH(C_2H_5)CH(C_2H_5)\text{-}C_6H_4O(PO)(OCH_2C_6H_5)_2$ / $(HO)_2(PO)OC_6H_4CH(C_2H_5)CH(C_2H_5)\text{-}C_6H_4O(PO)(OH)_2$

$HCOCOCH_3$ — $HCOCOCH_3$ — CH_3CO_2CH — $HCOCOCH_3$ — HC — $CH_2O(PO)(OCH_2C_6H_5)_2$ / $HCOCOCH_3$ — $HCOCOCH_3$ — CH_3CO_2CH — $HCOCOCH_3$ — HC — $CH_2O(PO)(OH)_2$

Note: References 84–105 are listed on pp. 325–326.

TABLE VIII
CARBOBENZYLOXY COMPOUNDS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
H₃CC(=CCOCH₃)–CCH₃ ; C₆H₅CH₂OCHNC=O ; NH *(structure)*	H₃CC(=CCOCH₃)–CCH₃ ; H₂NC ; NH *(structure)*	—	Pd black	CH₃OH + CH₃CO₂H	25	—	2–3 d.	125
H₃CC(=CCHO)–CCH₃ ; C₆H₅CH₂OCHNC=O ; NH *(structure)*	H₃CC(=CCH₂OH)–CCH₃ ; H₂NC ; NH *(structure)*	71	Pd black	CH₃OH + CH₃CO₂H	25	—	—	125
C₆H₅CH₂OCONHCH(CO₂H)CH₂C₆H₅	C₆H₅CH₂CH(NH₂)CO₂H	Quant.	Pd	—	—	—	—	45
C₆H₅CH₂OCONHCH(CO₂H)CH₂C₆H₄OH-p	p-HOC₆H₄CH₂CH(NH₂)CO₂H	Quant.	Pd	—	—	—	—	45
p-CH₃CO₂C₆H₄CH(CH₂C₆H₅)NHCO₂CH₂C₆H₅	p-HOC₆H₄CH₂CH(NH₂·HCl)CO₂CH₃	Quant.	Pd black	CH₃OH + HCl	25	1	—	47
C₆H₅CH₂OCONHCH(CONH₂)CH₂CO₂H	H₂NCH(CONH₂)CH₂CO₂H	Quant.	Pd	—	—	—	—	45
C₆H₅CH₂OCONHCH(CO₂H)CH₂CONH₂	H₂NCH(CO₂H)CH₂CONH₂	Quant.	Pd	—	—	—	—	45
C₆H₅CH₂OCONHCH(CONH₂)CH₂CH₂CO₂H	H₂NCH(CONH₂)CH₂CH₂CO₂H	Quant.	Pd	CH₃OH + CH₃CO₂H	—	—	—	45
C₆H₅CH₂OCONH(CH₂)₃CH(CO₂H)NHSO₂C₆H₅	H₂N(CH₂)₃CH(CO₂H)NHSO₂C₆H₅	—	Pd black	CH₃OH + HCl	—	—	—	126
C₆H₅CH₂OCONH(CH₂)₄CH(CONH₂)NHCOC₄H₆	H₂N(CH₂)₄CH(CONH₂)NHCOC₄H₆	—	Pd black	CH₃OH + HCl	—	—	—	126
CH₂–CH₂ / H₂C NCOCH₂NHCO₂CH₂C₆H₅ / CH₂–CH₂ *(piperidine structure)*	CH₂–CH₂ / H₂C NCOCH₂NH₂ / CH₂–CH₂ *(piperidine structure)*	—	Pd black	CH₃OH + HCl	—	—	—	127
C₆H₅CH₂OCONHCH(CH₃)CONHCH₂CO₂H	H₂NCH(CH₃)CONHCH₂CO₂H	95	Pd black	CH₃OH + CH₃CO₂H	—	—	30 min.	128
(CH₃)₂C(CO₂H)NHCOCH₂NHCO₂CH₂C₆H₅	(CH₃)₂C(CO₂H)NHCOCH₂NH₂	92	Pd black	CH₃OH + CH₃CO₂H	—	—	30 min.	128
(CH₃)₂C(CO₂H)NHCOCH(CH₃)NHCO₂CH₂C₆H₅	(CH₃)₂C(CO₂H)NHCOCH(CH₃)NH₂	Quant.	Pd black	CH₃OH + HCl	—	—	90 min.	128
(CH₃)₂C(NHCO₂CH₂C₆H₅)CONHCH₂CO₂CH₂C₆H₅	(CH₃)₂C(NH₂)CONHCH₂CO₂H	—	Pd black	Dil. CH₃CO₂H	—	—	—	128
HO₂CCH₂CH(CONHCH₂CO₂C₂H₅)NHCO₂CH₂C₆H₆	HO₂CCH₂CH(CONHCH₂CO₂C₂H₅)NH₂	90	Pd black	Ethanol + CH₃CO₂H	—	—	—	81
HO₂C(CH₂)₂CH(CONHCH₂CO₂C₂H₅)NH–CO₂CH₂C₆H₅	HO₂C(CH₂)₂CH(CONHCH₂CO₂C₂H₅)NH₂	89	Pd black	CH₃CO₂H	—	—	—	81
(CH₃)₂CHCH₂CH(CONHCH₂CO₂H)NHCO₂CH₂C₆H₅	(CH₃)₂CHCH₂CH(CONHCH₂CO₂H)NH₂	75	Pd black	—	—	—	—	81

Compound	Product		Catalyst	Solvent		30 min.	
(CH3)2CHCH2CH(NHCO2CH2C6H5)CONHCH(CH3)CO2H	(CH2)2CHCH2CH(NH2)CONHCH(CH3)CO2H	—	Pd black	CH3OH + CH3CO2H	—	—	128
C6H5CH2CH2O2CONHCH2CONHCH(CO2C2H5)(CH2)2CO2C2H5	H2NCH2CONHCH(CO2C2H5)(CH2)2CO2C2H5	—	Pd black	HCl	—	—	129
C6H5CH2OCONH(CH2)4CH(CO2C2H5)NHCOCH2NHCO2CH2C6H5	H2N(CH2)4CH(CO2CH3)NHCOCH2NH2	—	Pd black	CH3OH + HCl	—	—	126
C6H5CH2OCONH(CH2)4CH(CONH2)NHCOCH2NHCOC6H5	H2N(CH2)4CH(CONH2)NHCOCH2NHCOC6H5	—	Pd black	—	—	—	130
C6H5CH2OCONHCH(CH2CH2CO2H)CONHCH(CO2H)CH2CO2H	H2NCH(CH2CH2CO2H)CONHCH(CO2H)CH2CO2H	Quant.	Pd	—	—	—	45
O2NC(=NH)NH(CH2)3CH(CO2H)NHCOCH2NHCO2CH2C6H5	H2NC(=NH)NH(CH2)3CH(CO2H)NH-COCH2NH2	—	Pd black	—	—	—	131
O2NC(=NH)NH(CH2)2CH(CO2H)NHCOCH2NHCO2CH2C6H5	H2NC(=NH)NH(CH2)2CH(CO2H)NH-COCH2NH2	—	Pd black	HCl + CH3CO2H	—	—	132
C6H5CH2CH2OCONH(CH2)4CH(NHCO2CH2C6H5)CONHCH2CO2H	H2N(CH2)4CH(NH2)CONHCH2CO2H	35	Pd black	Ethanol + H2SO4	—	—	133
C6H5CONH(CH2)2CH(NHCO2CH2C6H5)CONHCH(CO2H)CH2CO2H	C6H5CONH(CH2)2CH(NH2)CONH-CH(CO2H)CH2CO2H	60	Pd black	CH3OH	—	—	133
C6H5CH2OCONH(CH2)4CH(NHCO2CH2C6H5)CONHCH(CO2H)CH2CO2H	H2N(CH2)4CH(NH2)CONHCH(CO2H)CH2CO2H	—	Pd black	Ethanol + CH3CO2H	—	—	133
[imidazole] HC=N, HN–CH ring, –CCH2CH(CO2H)NHCO(CH2)2NHCO2CH2C6H5	[imidazole] HC=N, HN–CH ring, –CCH2CH(CO2H)NHCO(CH2)3NH2 *	80	Pd black *	Dil. H2SO4	25	1	50
C6H5CH2OCONHCH2CONHCH(CONH2)CH2C6H4OH-p	H2NCH2CONHCH(CONH2)CH2C6H4OH-p	—	Pd black	—	—	—	134
p-CH3CO2C6H4CH2CH(NHCO2CH2C6H5)CONHCH2CO2C2H5	p-HOC6H4CH2CH(NH2)CONHCH2CO2C2H5	—	Pd black	CH3OH + HCl	—	—	134
p-CH3CO2C6H4CH2CH(NHCO2CH2C6H5)CONHCH(CO2H)CH2CO2H	p-HOC6H4CH2CH(NH2)CONH-CH(CO2H)CH2CO2H	95	Pd black	CH3OH + CH3CO2H	—	—	135
C6H5CH2OCONHCH(CH2CO2H)CONHCH(CO2H)CH2C6H4OH-p	H2NCH(CH2CO2H)CONH-CH(CO2H)CH2C6H4OH-p	Quant.	Pd	—	—	—	45
p-HOC6H4CH2CH(NHCO2CH2C6H5)CH2CO2H	p-HOC6H4CH2CH(CO2H)NHCO-CH(NH2)CH2CO2H	85	Pd black	Dil. CH3CO2H	—	—	135

Note: References 84–165 are listed on pp. 325–326.

* Hydrogenolysis with sodium in liquid ammonia gave equal yields of carnosine.

TABLE VIII—Continued
CARBOBENZYLOXY COMPOUNDS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
p-HOC₆H₄CH₂CH(NHCO₂CH₂C₆H₅)CO-NHCH(CO₂CH₃)CH₂C₆H₄OH-p	p-HOC₆H₄CH₂CH(NH₂)CO-NHCH(CO₂CH₃)CH₂C₆H₄OH-p	—	Pd black	—	25	1	—	47
p-HOC₆H₄CH₂CH₂CH(NHCO₂C₆H₅)CONH-CH(CO₂H)CH₂C₆H₄OH-p	p-HOC₆H₄CH₂CH(NH₂)CONH-CH(CO₂H)CH₂C₆H₄OH-p	Quant.	Pd black	CH₃OH + CH₃CO₂H	—	—	3–4 d.	135
p-HOC₆H₄CH₂CH(NHCO₂C₆H₅)CONH-CH(CO₂H)CH₂C₆H₄OH-p	p-HOC₆H₄CH₂CH(NH₂)CONH-CH(CO₂C₂H₅)CH₂C₆H₄OH-p	Quant.	Pd black	Ethanol + HCl	25	1	—	47
p-HOC₆H₄CO₂C₆H₄CH₂CH(NHCO₂CH₂C₆H₅)CONH-CH(CO₂C₂H₅)CH₂C₆H₄OH-p	CH(CO₂C₂H₅)CH₂C₆H₄OH-p	84	Pd black	Ethanol + CH₃CO₂H	—	—	—	81
HO₂CCH₂CH(CONHCH₂CO₂C₂H₅)NH-COCH₂NHCO₂CH₂C₆H₅	HO₂CCH₂CH(CONHCH₂CO₂C₂H₅)NH-COCH₂NH₂	93	Pd black	CH₃OH + CH₃CO₂H	—	—	—	81
HO₂CCH₂CH(CONHCH₂CO₂H)NHCOCH₂-NHCO₂CH₂C₆H₅	HO₂CCH₂CH(CONHCH₂CO₂H)NH-COCH₂NH₂	—	Pd black	HCl	—	—	—	129
C₆H₅CH₂OCONHCH₂CONHCH₂CONH-CH(CO₂C₂H₅)CH₂CH₂CO₂C₂H₅	H₂NCH₂CONHCH₂CONHCH(CO₂C₂H₅)CH₂-CH₂CO₂C₂H₅	—	Pd black	—	—	—	—	81
(CH₂)₂CHCH(CONHCH₂CO₂H)NHCOCH₂-NHCO₂CH₂C₆H₅	(CH₂)₂CHCH(CONHCH₂CO₂H)NH-COCH₂NH₂	—	Pd black	Ethanol + HCl	—	—	—	126
C₆H₅CH₂OCONH(CH₂)₄CH(CONHCH₂CO₂C₂H₅)NH-COCH₂NHCOC₆H₅	H₂N(CH₂)₄CH(CONHCH₂CO₂C₂H₅)NH-COCH₂NHCOC₆H₅	—	Pd black	CH₃OH + HCl	—	—	—	127
(CH₂)₂CHCH₂CHCONHCH(CONHCH₂CO₂H)-CH₂CH(CH₃)₂ / CH₂C₆H₄OCOCH₃-p	(CH₂)₂CHCH₂CHCONH-CH(CONHCH₂CO₂H)CH₂CH(CH₃)₂ / CH₂C₆H₄OH-p	—	Pd black	Dioxane + ethanol + HCl	25	1	—	47
C₆H₅CH₂OCONHCHCONHCH(CH₂C₆H₄OH-p)-CONHCH(CO₂C₂H₅)CH₂C₆H₄OH-p	H₂NCHCONHCH(CH₂C₆H₄OH-p)-CONHCH(CO₂C₂H₅)CH₂C₆H₄OH-p	—	Pd black	CH₃OH + CH₃CO₂H	—	—	—	81
C₆H₅CH₂OCONHCH₂CONHCH₂CONH-CH(CONHCH₂CO₂H)CH₂CH(CH₃)₂	H₂NCH₂CONHCH₂CONH-CH(CONHCH₂CO₂H)CH₂CH(CH₃)₂	—	Pd black	CH₃OH + CH₃CO₂H	—	—	—	81
C₆H₅CH₂OCONHCH₂CONHCH₂CONHCH₂-CONHCH(CONHCH₂CO₂H)CH₂CH(CH₃)₂ / NHCO₂CH₂C₆H₅	H₂N(CH₂)₃CH(CONHCH₂CO₂H)-CH₂CH(CH₃)₂ / NH₂	—	Pd black	HCl	—	—	—	129
C₆H₅CH(CH₂OCONH(CH₂)₄CH(CONHCH₂)₂CO-NHCH(CO₂C₂H₅)CH₂CH₂CO₂C₂H₅	H₂NCH(CH₂)₄CH(CONHCH₂)₂CO-NHCH(CO₂C₂H₅)CH₂CH₂CO₂C₂H₅							

Compound	Yield %	Catalyst	Solvent	Temp.	Pressure	Time	Ref.
NHCO₂CH₂C₆H₅ p-CH₃CO₂C₆H₄CH₂CH-CO]NHCH(CH₂C₆H₄OH-p)CO]₂NH- CH(CO₂H)CH₂C₆H₄OH-p is reduced to NH₂ p-HOC₆H₄CH₂CH-CO]NHCH(CH₂C₆H₄OH-p)CO]₂NH- CH(CO₂H)CH₂C₆H₄OH-p	—	Pd black	CH₃OH + CH₃CO₂H	25	1	30 min.	47
C₆H₅CH₂OCONHCH₂CO₂H + C₆H₅CH₂CH₂C₆H₅	95	Na	Liquid NH₃	—	—	—	50
H₂NCH₂CH₂CO₂H + C₆H₅CH₂CH₂C₆H₅	95	Na	Liquid NH₃	—	—	—	50
SCH₂CH(CO₂H)NHCO₂CH₂C₆H₅ is reduced to HSCH₂CH(CO₂H)NH₂	89	PdO	CH₃CO₂H	25	1	1-0 d.	130
SCH₂CH(CO₂H)NHCO₂CH₂C₆H₅ (CH₃)₂CHCH₂CH(NHCO₂CH₂C₆H₄)CONHCH₂- CONHCH₂CO₂H	40	Pd-charcoal	Ethanol + HCl	25	4	2 hr.	137
o-C₆H₅CH₂OCONHCH₂CO₂C₆H₄CO₂CH₃	67	Pd black	Ethanol + HCl	25	1	9 hr.	138
H₂NCH₂CO₂C₆H₅	83	Pd black	Ethanol + HCl	25	1	6 hr.	138
C₆H₅CH₂OCONHCH₂CONHCH₂CO₂C₆H₅	75	Pd black	Ethanol + HCl	25	1	2 hr.	138
C₆H₅CH₂OCONHCH₂CONHCH₂CO₂C₆H₅	61	Pd black	Ethanol + HCl	25	1	4 hr.	138
C₆H₅CH₂O₂CONHCH₂CONHCH₂CONHCH₂CO₂C₆H₅ H₂NCH₂CONHCH₂CONHCH₂CO₂C₁₇H₂₀O₂N H₂NCH₂CO₂C₁₇H₂₀O₂N (glycyldihydromorphine) p-CH₃CO₂C₆H₄CH₂CH(NH₂)CO₂C₁₇H₂₀O₂N (O-acetyl-L-tyrosyldihydromorphine)	—	Pd black	Ethanol + HCl	25	1	1 hr.	138
C₆H₅CH₂O₂CONHCH₂CONHCH(CH₂C₆H₄NHCO₂CH₂C₆H₅)- CO₂C₁₇H₁₈O₂N (carbobenzyloxyglycyclmorphine) p-CH₃CO₂C₆H₄CH₂CH(NHCO₂CH₂C₆H₅)- CO₂C₁₇H₁₈O₂N (0-acetylcarbobenzyloxy-L-tyrosylmorphine)	—	—	—	—	—	—	139
(CH₃)₂CHCH₂OCONHCH(CH₂CH₂CH₂NHCO₂CH₂C₆H₅)CONHCH(CH₂C₆H₅)CONHCH(CH₂CH(CH₃)₂ CH₂—CH₂ CH₂—CH₂ CH—CH₂ O= CN CH—CO₂CH₃ CH₂CH(CH₃)₂							
NHCO₂CH₂C₆H₅ NH₂ CH—CH₂ CH₂—CH₂ O= CN CH—CH₂ CO₂CH₃							
(CH₃)₂CHCH(NHCO₂CH₂CH₂CH₂)CONHCH(CO₂H)- CH₂CH₂NHCO₂CH₂C₆H₅ (CH₃)₂CHCH(NH₂)CONHCH(CO₂H)CH₂- CH₂CH₂NH₂	Quant.	Pd sponge	CH₃CO₂H + HCl + CH₃OH	25	1	—	140

Note: References 84–105 are listed on pp. 325–326.

TABLE VIII—*Continued*

CARBOBENZYLOXY COMPOUNDS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
$C_6H_5CH_2OCONH(CH_2)_3CHNHCO_2CH_2C_6H_5CO-NHCH(CO_2H)CH_2CH(CH_3)_2$	$H_2N(CH_2)_3CH(NH_2)CONHCH(CO_2H)CH_2-CH(CH_3)_2$	64	Pd sponge	$CH_3CO_2H + HCl$	25	1	—	140
$(CH_3)_2CHCH_2CH(NHCO_2CH_2C_6H_5)CONH-CH(CH_2C_6H_5)CO_2H$	$(CH_3)_2CHCH_2CH(NH_2)CONH-CH(CH_2C_6H_5)CO_2H$	78	Pd sponge	$CH_3CO_2H + CH_3OH$	25	1	—	140
(structure: ring CH_2—CH_2 / CH_2 / N / $CO_2C_6H_5$; CHCONHCH(CO₂H)CH(CH₃)₂)	(structure: ring CH_2—CH_2 / CH_2 / N H; CHCONHCH(CO₂H)CH(CH₃)₂)	81	Pd sponge	$CH_3CO_2H + CH_3OH$	25	1	—	140
(structure with ring, CH_2—CH_2, CH—CH_2, O, CN, CO_2H; $C_6H_5CH_2CHNHCO_2CH_2C_6H_5$)	(structure with ring, CH_2—CH_2, CH—CH_2, O, CN, CO_2H; $C_6H_5CH_2CH(NH_2)CN$)	83	Pd sponge	$CH_3CO_2H + CH_3OH$	25	1	—	140
$p-H_2NC(=NH)NHC_6H_4OCH$ / $HCNHCO_2CH_2C_6H_5$ / CH_3CO_2H / $HCOCOCH_3$ / HC / CH_2OCOCH_3 (ring with O)	$p-H_2NC(=NH)NHC_6H_4OCH$ / $HCNH_2$ / CH_3CO_2H / $HCOCOCH_3$ / HC / CH_2OCOCH_3 (ring with O)	Quant.	Pd-charcoal	CH_3OH	—	1	6-8 hr.	141

$2,4\text{-}[H_2NC(=NH)NHl_2C_6H_3OCH$
HCNHCO_2CH_2C_6H_5
CH_3CO_2CH
HCOCOCH_3
HC
CH_2OCOCH_3

$2,4\text{-}[H_2NC(=NH)NHl_2C_6H_3OCH$
HCNH_2
CH_3CO_2CH
HCOCOCH_3
HC
CH_2OCOCH_3

60   Pd-charcoal   H_2O   —   1   6 hr.   141

$2,4\text{-}(H_2N)_2C_6H_3OCH$
HCNHCO_2CH_2C_6H_5
CH_3CO_2CH
HCOCOCH_3
HC
CH_2OCOCH_3

$2,4\text{-}(H_2N)_2C_6H_3OCH$
HCNH_2
CH_3CO_2CH
HCOCOCH_3
HC
CH_2OCOCH_3

50–70   Pd-charcoal   CH_3OH + CH_3CO_2C_2H_5   —   1   3 hr.   141

HCOCH_3
HCNHCO_2CH_2C_6H_5
HOCH
HCOH
HC
CH_2OH

HCOCH_3
HCNH_2
HOCH
HCOH
HC
CH_2OH

98   Pd black   Ethanol + HCl   —   —   —   142

Note: References 84–165 are listed on pp. 325–326.

TABLE VIII—Continued

Carbobenzyloxy Compounds

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm	Time	Reference
$\begin{array}{l} \text{OH} \\ \text{HC} \\ \text{HCNHCOCH(CH}_3\text{)NHCO}_2\text{CH}_2\text{C}_6\text{H}_5 \\ \text{HOCH} \\ \text{HCOH} \\ \text{HC} \\ \text{CH}_2\text{OH} \end{array}$	$\begin{array}{l} \text{OH} \\ \text{HC} \\ \text{HCNHCOCH(CH}_3\text{)NH}_2 \\ \text{HOCH} \\ \text{HCOH} \\ \text{HC} \\ \text{CH}_2\text{OH} \end{array}$	Quant.	Pd black	Dil. CH₃OH	25	1	15 min.	46
$\begin{array}{l} \text{OH} \\ \text{HC} \\ \text{HCNHCOCH}_2\text{NHCO}_2\text{CH}_2\text{C}_6\text{H}_5 \\ \text{HOCH} \\ \text{HCOH} \\ \text{HC} \\ \text{CH}_2\text{OH} \end{array}$	$\begin{array}{l} \text{OH} \\ \text{HC} \\ \text{HCNHCOCH}_2\text{NH}_2 \\ \text{HOCH} \\ \text{HCOH} \\ \text{HC} \\ \text{CH}_2\text{OH} \end{array}$	Quant.	Pd black	Dil. CH₃OH	25	1	15 min.	46

Note: References 84–165 are listed on pp. 325–326.

TABLE IX

MONODEBENZYLATION TO PRIMARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm	Time	Reference
$C_6H_5NHCH_2C_6H_5$	$C_6H_{11}CH_3NH_2 + C_6H_{11}NHCH_2C_6H_{11}$	—	H_2PtCl_6	CH_3CO_2H	—	—	—	7
$C_6H_5NHCH_2C_6H_5$	$C_6H_5CH_3 + C_6H_5NH_2$	Quant.	Pd-charcoal	Ethanol	25	1	—	13
$C_6H_5NHCH_2C_6H_5$	$C_6H_5CH_3 + C_6H_5NH_2$	Quant.	PdO	CH_3CO_2H	—	1	—	51
$o\text{-}HOC_6H_4CH_2NHC_6H_5$	$o\text{-}HOC_6H_4CH_3 + C_6H_5NH_2$	Quant.	Pd-charcoal	Ethanol	25	1	—	13
$3,4\text{-}(CH_2O_2)C_6H_3CH_2NHCH_2C_6H_5$	$3,4\text{-}(CH_2O_2)C_6H_3CH_3 + C_6H_5NH_2$	Quant.	Pd-charcoal	Ethanol	25	1	—	13
$\alpha\text{-}C_{10}H_7NHCH_2C_6H_5$	$\alpha\text{-}C_{10}H_7NH_2 + C_6H_5CH_3$	88	PdO	CH_3CO_2H	—	—	—	51
$C_6H_5CH_2NH(CH_2)_3CH(CH_3)N(CH_3)_2$	$H_2N(CH_2)_3CH(CH_3)N(CH_3)_2$	—	—	—	—	—	—	53
(indole structure, CH_3, $CH_2NHCH_2C_6H_5$)	(indole structure, CH_3, $CH_2CH_2NH_2$)	—	—	Neutral	—	—	—	53
$C_6H_5CH_2NHCH_2CH_2CO_2C_2H_5$	$H_2NCH_2CH_2CO_2C_2H_5$	Quant.	Pd-Pt-charcoal	Ethanol	25	13	—	55
$CH_3CH(CH_2OH)NHCH_2C_6H_5$	$CH_3CH(NH_2)CH_2OH$	—	Pd	—	—	—	—	56
$C_2H_5CH(CH_2OH)NHCH_2C_6H_5$	$C_2H_5CH(NH_2)CH_2OH$	—	Pd	—	—	—	—	56
$(CH_3)_2CHCH_2CH(CH_2OH)NHCH_2C_6H_5$	$(CH_3)_2CHCH_2CH(NH_2)CH_2OH$	—	Pd	—	—	—	—	56
$C_6H_5CH_2NHCH(CH_2OH)CO_2H$	$H_2NCH(CH_2OH)CO_2H$	90	Pd-charcoal	Ethanol	25	13	3 hr.	143
(indane structure, $NHCH_2C_6H_5$, OH)	(indane structure, NH_2, OH)	—	PtO_2	Ethanol	25	3	—	144
$C_6H_5CH_2NHCH(CO_2H)CH(CO_2H)NHCH_2C_6H_5$	$H_2NCH(CO_2H)CH(CO_2H)NH_2$	90	Pd-charcoal	CH_3CO_2H + HCl	20-35	50	36 hr.	57
$CH_3(CH_2)_3CH(NHCH_2C_6H_5)CH_2OH$	$CH_3(CH_2)_3CH(NH_2)CH_2OH$	—	Pd-charcoal	CH_3OH	25	1	16 hr.	58

Note: References 84–165 are listed on pp. 325–326.

TABLE IX—Continued

MONODEBENZYLATION TO PRIMARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
CH2CONHCH2C6H5 — CHCO2H — NHCH2C6H5	CH2CONHCH2C6H5 — CHCO2H — NH2	90	Pd-charcoal	CH3CO2H	60	—	3 hr.	145
CH2—C=O, CH—C=O (ring, NCH2C6H5) — NHCH2C6H5	CH2—C=O, CH—C=O (ring, NCH2C6H5) — NH2	—	Pd-charcoal	CH3CO2H	50	—	25 min.	145

Note: References 84–165 are listed on pp. 325–326.
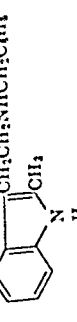
TABLE X

DIDEBENZYLATION TO PRIMARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
(C6H5CH2)2NCN	H2NCN	—	PdO	Ethanol	—	—	—	51
(C6H5CH2)2NCH2CH2OC6H5	C6H5OCH2CH2NH2	—	—	—	—	—	—	53
(C6H5CH2)2NCH2CH2NHC6H5	C6H5NHCH2CH2NH2	—	—	—	—	—	—	53
(α-C10H7CH2)2NCH2CH2N(CH3)CH2CH2OH	H2NCH2CH2N(CH3)CH2CH2OH	Quant.	Pd-charcoal	Ethanol	25	1	—	13
(C6H5CH2)2NC6H5	C6H5NH2	—	Pd	—	—	—	—	53
(C6H5CH2)2NCH2CH2CH(CO2C2H5)2	H2NCH2CH2CH2CO2C2H5	—	—	—	—	—	—	53
(C6H5CH2)2NCH2CO2H	H2NCH2CO2H	95	PdO	CH3CO2H	—	—	—	51
(C6H5CH2)2NCH2CO2CH3	H2NCH2CO2CH3	96	PdO	CH3CO2H	—	—	—	51
C6H5COCH2N(CH2C6H5)2·HCl	C6H5COCH2NH2	—	Pd-charcoal	H2O	25	1	—	111
3,4-(HO)2C6H3COCH2N(CH2C6H5)2·HCl	3,4-(HO)2C6H3COCH2NH2	85	Pd-charcoal *	H2O	25	10	5 hr.	146
p-HOC6H4COCH2N(CH2C6H5)2·HCl	p-HOC6H4CHOHCH2NH2	86	Pd-charcoal	Ethanol	25	10	1 hr.	146

Note: References 84–165 are listed on pp. 325–326.

* With a higher ratio of catalyst to amine the carbonyl group was reduced to a hydroxyl group.

TABLE XI

MONODEBENZYLATION OF DIBENZYL TERTIARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temper- ature °C	Pres- sure	Time	Refs.
$(C_6H_5CH_2)_2NCH_2CH_2CH_2COCH_3$	$C_6H_5CH_2NHCH_2CH_2CH_2COCH_3$	—	Pd	—	—	—	—	53
CHOHCH₂N(CH₂C₆H₅)₂	CHOHCH₂NHCH₂C₆H₅	—	Pd-charcoal	—	—	—	—	54
COCH₂N(CH₂C₆H₅)₂	COCH₂NHCH₂C₆H₅	—	Palladized	—	—	—	—	54
CH₂CH₂N(CH₂C₆H₅)₂	CH₂CH₂NHCH₂C₆H₅	—	—	—	—	—	—	55
		73	PtO	Ethanol	—	—	—	56

Note: References 84–165 are listed on pp. 325–326.

TABLE XII

COMPETITIVE DEBENZYLATIONS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
p-CH$_3$C$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_5$·HCl	p-CH$_3$C$_6$H$_4$CH$_2$NHCH$_3$·HCl	Quant.	Pd-charcoal	CH$_3$OH	25	3	—	16
p-ClC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_5$·HCl	p-ClC$_6$H$_4$CH$_2$NHCH$_3$·HCl	—	Pd-charcoal	CH$_3$OH	25	3	—	16
p-CH$_3$OC$_6$H$_4$CH$_2$NHCH$_2$C$_6$H$_5$·HCl	p-CH$_3$OC$_6$H$_4$CH$_2$NH$_2$·HCl	Quant.	Pd-charcoal	Ethanol	65	3	—	16
m-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$OCH$_3$-p·HCl	m- and p-CH$_3$OC$_6$H$_4$CH$_2$NHCH$_3$·HCl	—	Pd-charcoal	Ethanol	25	3	—	16
o- and p-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$OCH$_3$-p·HCl	o- and p-CH$_3$OC$_6$H$_4$CH$_2$NHCH$_3$·HCl	Quant.	Pd-charcoal	Ethanol	65	3	—	16
3,4-(CH$_3$O$_2$)C$_6$H$_3$CH$_2$NHCH$_2$C$_6$H$_4$OCH$_3$-p·HCl	3,4-(CH$_3$O$_2$)C$_6$H$_3$CH$_2$NH$_2$·HCl	Quant.	Pd-charcoal	Ethanol + HCl	75	3	—	16
p-CH$_3$OC$_6$H$_4$CH$_2$N=CHC$_6$H$_4$OCH$_2$C$_6$H$_5$-p·HCl	p-CH$_3$OC$_6$H$_4$CH$_2$NH$_2$·HCl + p-HOC$_6$H$_4$CH$_3$	—	Pd-charcoal	Ethanol	75	3	—	16
p-CH$_3$OC$_6$H$_4$CH$_2$NHCH$_2$C$_6$H$_4$OH-p·HCl	p-CH$_3$OC$_6$H$_4$CH$_2$NH$_2$·HCl + p-HOC$_6$H$_4$CH$_3$	—	Pd-charcoal	Ethanol	75	3	—	16
p-O$_2$NC$_6$H$_4$CH$_2$NHCH$_2$C$_6$H$_5$·HCl	p-H$_2$NC$_6$H$_4$CH$_2$NHCH$_3$·2HCl *	—	Pd-charcoal	Ethanol	25	3	—	16
p-Cl(CH$_3$)$_3$NC$_6$H$_4$CH$_2$NHCH$_2$C$_6$H$_5$·HCl	p-Cl(CH$_3$)$_3$NC$_6$H$_4$CH$_2$NH$_2$·HCl	—	Pd-charcoal	Ethanol	75	3	—	16
[α-C$_{10}$H$_7$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$C$_6$H$_5$-p]·HCl	α-C$_{10}$H$_7$CH$_2$NHCH$_3$·HCl + p-C$_6$H$_5$C$_6$H$_4$CH$_2$NHCH$_3$·HCl	—	Pd-charcoal	CH$_3$OH	25	3	—	16
α-C$_{10}$H$_7$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_5$·HCl	C$_6$H$_5$CH$_2$NHCH$_3$·HCl	Quant.	Pd-charcoal	CH$_3$OH	25	3	—	16
β-C$_{10}$H$_7$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_5$·HCl	C$_6$H$_5$CH$_2$NHCH$_3$·HCl	Quant.	Pd-charcoal	CH$_3$OH	25	3	—	16
α-C$_{10}$H$_7$CH$_2$N(CH$_3$)CH$_2$C$_{10}$H$_7$-β·HCl	α- and β-C$_{10}$H$_7$CH$_2$NHCH$_3$·HCl	Quant.	Pd-charcoal	CH$_3$OH	25	3	—	16
p-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$Cl-p·HCl	p-CH$_3$OC$_6$H$_4$CH$_2$NHCH$_3$·HCl	—	Pd-charcoal	Ethanol	65	3	Slow †	59, 147
[p-ClC$_6$H$_4$CH$_2$N(CH$_3$)$_2$CH$_2$C$_6$H$_4$Cl-p]Cl	p-ClC$_6$H$_4$CH$_2$N(CH$_3$)$_2$·HCl	50	Pd-charcoal	Abs. ethanol	25	3	Moderate †	59, 147
p-CH$_3$O$_2$CC$_6$H$_4$CH$_2$N(CH$_3$)CH$_2$C$_6$H$_4$CO$_2$CH$_3$-p·HCl	p-CH$_3$C$_6$H$_4$CO$_2$CH$_3$ p-CH$_3$O$_2$CC$_6$H$_4$CH$_2$NHCH$_3$·HCl	30 30	Pd-charcoal	CH$_3$OH	65	3	Slow †	59, 147

Substrate	Product	%	Catalyst	Solvent	Temp (°C)	Moles	Rate	References
[p-CH₃OC₆H₄CH₂N(CH₃)₂CH₂C₆H₄NHCOCH₃-p]Cl	p-CH₃CONHC₆H₄CH₃	40	Pd-charcoal	CH₃OH	25	3	Fast †	59, 147
	p-CH₃CONHC₆H₄CH₂N(CH₃)₂·HCl	30						
	p-CH₃OC₆H₄CH₂N(CH₃)₂·HCl	10						
	p-CH₃C₆H₄NH₂·HCl	70						
	p-CH₃OC₆H₄CH₂NHCH₃·HCl	90						
p-CH₃OC₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-p·HCl	[p-CH₃OC₆H₄CH₂N(CH₃)CH₂C₆H₄NH₂-p]2HCl	—	Pd-charcoal	CH₃OH	25	3	Moderate †	59, 147
p-CH₃OC₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-p	p-CH₃C₆H₄NH₂·HCl	80	Pd-charcoal	CH₃OH + 10 eq. HCl	65	3	Fast †	59, 147
[p-CH₃OC₆H₄CH₂N(CH₃)₂CH₂C₆H₄NH₂-p]Cl₂	p-CH₃OC₆H₄CH₂N(CH₃)₂·HCl	90	Pd-charcoal	CH₃OH + HCl	25	3	Moderate †	59, 147
	p-ClC₆H₄CH₂NHCH₃·HCl	85–90	Pd-charcoal	CH₃OH	25	3	Slow †	59, 147
p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-p·HCl	p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄CO₂CH₃-p·HCl	70	Pd-charcoal	CH₃OH	25	3	Slow †	59, 147
	p-CH₃O₂CC₆H₄C₆H₃	10						
	p-CH₃C₆H₄NH₂·HCl	95–100	Pd-charcoal	CH₃OH	25	3	Slow †	59, 147
	p-CH₃C₆H₄CH₂N(CH₃)CH₂C₆H₄NHCH₃·HCl	65–70						
p-H₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄NO₂-p·HCl	p-H₂NC₆H₄CH₂NHCH₃·2HCl	15	Pd-charcoal	CH₃OH + 20 eq. HCl	65	3	Slow †	59, 147
p-O₂NC₆H₄CH₂N(CH₃)CH₂C₆H₄Cl-p HCl	C₆H₅CH₂NHCH₃·HCl	20	Pd-charcoal	CH₃OH	25	3	Slow †	59, 147
	p-CH₃C₆H₄NH₂·HCl	60						

Note: References 84–165 are listed on pp. 325–326.

* When 13 moles of hydrogen chloride was present, the benzyl group was not removed; when 34 moles of hydrogen chloride was present, the benzyl group was removed.

† Although the approximate times for reduction are included where known, the value of this information is only relative for the total time is a function of many factors, among which must be the amounts of catalyst and substrate. Rarely is the rate of reduction a straight line function of time. For the examples cited in the above table, Baltzly[147] considers that during an early stage of debenzylation an absorption of 1 mmole/5 min. or less is slow; 1 mmole/3 min. is moderate, and 1 mmole/1 min. to 1 mmole/1 min. is fast; and any absorption taking place more rapidly is fast.

TABLE XIII

MONOBENZYLATION TO SECONDARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
2,5-Di(dimethylaminomethyl)hydroquinone	2,5-Dimethylhydroquinone + $(CH_3)_2NH$	23	Copper chromium oxide	Dioxane	165	170	4 hr.	61
2-Dimethylaminomethyl-3,5-dimethylphenol	2,3,5-Trimethylphenol + $(CH_3)_2NH$	58	Copper chromium oxide	Dioxane	165	177	4 hr.	61
$C_2H_5CH_2N(CH_3)C_2H_4$	$CH_3NHC_2H_5$	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(CH_3)C_3H_7$-n	$CH_3NHC_3H_7$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(CH_3)C_4H_{11}$-$n$	$CH_3NHC_4H_{11}$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(CH_3)C_7H_{15}$-$n$	$CH_3NHC_7H_{15}$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(CH_3)C_6H_{13}$-$n$	$CH_3NHC_6H_{13}$-n	92	PdO	CH_3CO_2H	—	1	—	51
$C_2H_5CH_2N(C_2H_5)C_3H_7$-$n$	$C_2H_5NHC_3H_7$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(C_2H_5)C_6H_9$-$n$	$C_2H_5NHC_6H_9$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(C_2H_5)C_6H_{11}$-$n$	$C_2H_5NHC_6H_{11}$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(C_3H_7$-$n)C_4H_9$-n	n-$C_3H_7NHC_4H_9$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$C_2H_5CH_2N(C_4H_9$-$n)C_6H_{11}$-n	n-$C_4H_9NHC_6H_{11}$-n	—	PtO_2	CH_3CO_2H	65-75	3	8 hr.	52
$(n$-$C_6H_{13})_2NH$	$(n$-$C_6H_{13})_2NH$	Quant.	PtO_2	CH_3CO_2H	70	—	6 hr.	60
$C_2H_5CH_2N(C_7H_{15}$-$n)_2$	$(n$-$C_7H_{15})_2NH$	Quant.	PtO_2	CH_3CO_2H	70	—	6 hr.	60
$C_2H_5CH_2N(C_{12}H_{25}$-$n)_2$	n-$C_6H_{11}CH_2N(C_{12}H_{25}$-$n)_2$	84	PtO_2	CH_3CO_2H	—	—	—	51
$C_6H_5N(CH_3)CH_2C_6H_5$	$C_6H_5NHCH_3$	Quant.	Pd-charcoal	Ethanol	25	1	—	13
$C_6H_5N(C_2H_5)CH_2C_6H_5$	$C_6H_5NHC_2H_5$	Quant.	Pd-charcoal	Ethanol	25	1	—	13
(N-substituted indoline structure)	(indole structure)	—	—	—	—	—	—	53
$C_6H_5CHOHCH(CH_3)N(CH_3)CH_2C_6H_5$	$C_6H_5CHOHCH(CH_3)NHCH_3$	Quant.	PtO_2	Ethanol	25	1	—	148
$2,5$-$(CH_3O)_2C_6H_3C(OH)(CH_3)CH_2N(CH_3)CH_2C_6H_5$	$2,5$-$(CH_3O)_2C_6H_3C(OH)(CH_3)CH_2NHCH_3$	—	—	—	—	—	—	149

Compound	Yield (%)	Catalyst	Solvent			Time	Ref.
(benzofuran) CHOHCH₂N(CH₃)CH₂C₆H₅ / CHOHCH₂NHCH₃	—	Pd-charcoal	—	—	—	—	54
p-HOC₆H₄COCH₂N(CH₃)CH₂C₆H₅·HCl / p-HOC₆H₄CHOHCH₂NHCH₃·HCl	85	Nickel	H₂O	80–90	40	—	150
3-F-4-HOC₆H₃COCH₂N(CH₃)CH₂C₆H₅·HCl / 3-F-4-HOC₆H₃CHOHCH₂NHCH₃·HCl	95	Pt black	Abs. CH₃OH	25	3	1 hr.	151
3-Cl-4-HOC₆H₃COCH₂N(CH₃)CH₂C₆H₅·HCl / 3-Cl-4-HOC₆H₃CHOHCH₂NHCH₃·HCl	—	Pt black	Abs. CH₃OH	25	3	12 hr.	151
3,4-(HO)₂C₆H₃COCH₂N(CH₃)CH₂C₆H₅ / 3,4-(HO)₂C₆H₃CHOHCH₂NHCH₃	—	Pd-acacia	2 N HCl	25	1	8–12 hr.	152
C₆H₅COCH₂N(CH₃)CH₂C₆H₅·HCl / C₆H₅CHOHCH₂NHCH₃·HCl	—	Nickel	H₂O	90	50	—	150
C₆H₅COCH(CH₃)N(CH₃)CH₂C₆H₅ / C₆H₅CHOHCH(CH₃)NHCH₃	—	Ni:Co:Cu, 10:6:1	H₂O	90–100	40	1 hr.	150
C₆H₅COCH₂N(CH₃)CH₂C₆H₅·HCl / C₆H₅CHOHCH₂NHCH₃·HCl	—	Ni:Co, 3:1	H₂O	90	50	—	150
C₆H₅COCH(CH₃)N(CH₃)CH₂C₆H₅ / C₆H₅CHOHCH(CH₃)NHCH₃	—	Nickel	Dil. ethanol	90–100	40	1 hr.	152
C₆H₅COCH(CH₃)N(CH₃)CH₂C₆H₅ / C₆H₅CHOHCH(CH₃)NHCH₃	—	Pd black	Dil. ethanol	25	1	—	152
C₆H₅COCH(CH₃)N(CH₃)CH₂C₆H₅ / C₆H₅CHOHCH(CH₃)NHCH₃	—	Pd-acacia	2 N HCl	25	1	—	152
C₆H₅COCH(C₂H₅)N(CH₃)CH₂C₆H₅ / C₆H₅CHOHCH(C₂H₅)NHCH₃	—	Pd	—	—	—	—	27
(piperazine structure: CH₂CH₂ / NCH₂C₆H₅ … CNH₂ → NH)	92	PdO	CH₃CO₂H	—	—	—	51
(piperazine structure)	95	PdO	CH₃CO₂H	—	—	—	51
(guanidine/triazine structure: C₆H₅CH₂CN, HN=C, C=NH, N—CH₂C₆H₅ → C=NH, C—N—H)	94	PdO	Ethanol	—	—	—	51
(C₆H₅CH₂)₂NCH₂CH₂CH₂COCH₃ / C₆H₅CH₂NHCH₂CH₂CH₂CH(CH₃)NH₂	—	Nickel	NH₃	—	—	—	53
2,5-(CH₃O)₂C₆H₃COCH₂N(CH₃)CH₂C₆H₆ / 2,5-(CH₃O)₂C₆H₃CHOHCH₂NHCH₃	—	PtO₂	—	—	—	—	149

Note: References 84–165 are listed on pp. 325–326.

TABLE XIII—Continued

MONODEBENZYLATION TO SECONDARY AMINES

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
(COCH₂N(CH₃)CH₂C₆H₅ on benzofuran)	$COCH_2NHCH_3$ on benzofuran	—	Pd-charcoal	—	—	—	—	54
$(C_6H_5CH_2)_3N$	$(C_6H_5CH_2)_2NH$	97	PdO	Ethanol	—	1	—	51
α(CON(CH₃)₂ CH₂N(CH₃)CH₂C₆H₅) pyridine	OCON(CH₃)₂ CH₂NHCH₃ pyridine	—	Pd-charcoal	CH₃OH	25	1	140 min.	153
$3,5\text{-}(CH_3O)_2C_6H_3COCH_2N(CH_3)CH_2C_6H_5$	$3,5\text{-}(CH_3O)_2C_6H_3COCH_2NHCH_3$	87–94	Pd	Ethanol	45	—	—	154
		92–98	Pd sponge	Ethanol	50	—	—	155, 156
		—	Pd-charcoal	CH₃OH	—	—	—	157

Note: References 84–163 are listed on pp. 325–326.

TABLE XIV—*Continued*

SIMULTANEOUS O- AND N-DEBENZYLATION

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C	Pressure atm.	Time	Reference
$C_2H_5CH_2OCONHCH_2COOC-H$ $HC-OCOCH_2NHCO_2CH_2C_6H_5$ $HC-OCOCH_2NHCO_2CH_2C_6H_5$ (structure)	$HCOCOCH_2NH_2$ $HCOCOCH_2NH_2$ H_2NCH_2COOH $HCOH$ $HC-O$ CH_2OH	Quant.	Pd black	Dil. CH₃CO₂H + H₂SO₄	—	—	—	159
CO_2H $C_6H_5CH_2OCONHCH$ $HOCH$ $HCOH$ HCO CH_2O (structure with CHC_6H_5)	CO_2H H_2NCH $HOCH$ $HCOH$ $HCOH$ CH_2OH	60	Pd black	CH₃OH + CH₃CO₂H	—	—	—	160
p-$C_6H_5CH_2OC_6H_4COCH_2N(CH_3)CH_2C_6H_5$	p-HOC₆H₄COCH₂NHCH₃	—	—	—	—	—	—	161

Note: References 84–163 are listed on pp. 325–326.

TABLE XV

QUATERNARY AMMONIUM COMPOUNDS

Substance Reduced	Product Isolated	Yield %	Catalyst	Solvent	Temperature °C.	Pressure atm.	Time	Reference
[(C$_6$H$_5$CH$_2$)$_3$N(CH$_3$)]OH	C$_6$H$_5$CH$_2$NHCH$_3$	—	PdO	Ethanol	—	—	—	51
[C$_6$H$_5$CH$_2$N(CH$_3$)$_2$C$_6$H$_5$]Cl	C$_6$H$_{11}$N(CH$_3$)$_2$	—	PdO	Ethanol	—	—	—	51

Note: References 84–165 are listed on pp. 325–326.

TABLE XVI

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY [24]

Substance Reduced	Product Isolated	Yield %
C$_6$H$_5$CH$_2$OH	C$_6$H$_5$CH$_3$	70
C$_6$H$_5$CHO	C$_6$H$_5$CH$_3$	60
o-HOC$_6$H$_4$CH$_2$OH	o-HOC$_6$H$_4$CH$_3$	85
o-HOC$_6$H$_4$CHO	o-HOC$_6$H$_4$CH$_3$	75
p-HOC$_6$H$_4$CHO	p-HOC$_6$H$_4$CH$_3$	80
C$_6$H$_5$COCH$_3$	C$_6$H$_5$C$_2$H$_5$	70
m-O$_2$NC$_6$H$_4$COCH$_3$	m-H$_2$NC$_6$H$_4$C$_2$H$_5$	76
p-HOC$_6$H$_4$COCH$_3$	p-HOC$_6$H$_4$C$_2$H$_5$	72
p-HOC$_6$H$_4$COC$_2$H$_5$	p-HOC$_6$H$_4$CH$_2$C$_2$H$_5$	78
p-HOC$_6$H$_4$COC$_6$H$_5$	p-HOC$_6$H$_4$CH$_2$C$_6$H$_5$	90
C$_6$H$_5$COCH$_2$C$_6$H$_5$	C$_6$H$_5$CH$_2$CH$_2$C$_6$H$_5$	70
C$_6$H$_5$CHOHCOC$_6$H$_5$	C$_6$H$_5$CH$_2$CH$_2$C$_6$H$_5$	50

REFERENCES TO TABLES I–XVII

[84] Nightingale and Radford, *J. Org. Chem.*, **14**, 1089 (1949).

[85] Reeve and Sterling, *J. Am. Chem. Soc.*, **71**, 3657 (1949).

[86] Johnson, Goldman, and Schneider, *J. Am. Chem. Soc.*, **67**, 1357 (1945).

[87] Johnson and Jones, *J. Am. Chem. Soc.*, **69**, 792 (1947).

[88] Kindler and Kwok, *Ann.*, **554**, 9 (1943).

[89] Kindler and Schrader, *Ann.*, **564**, 49 (1949).

[90] Miller, Hartung, Rock, and Crossley, *J. Am. Chem. Soc.*, **60**, 7 (1938).

[91] Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 1295 (1940).

[92] Fieser and Daudt, *J. Am. Chem. Soc.*, **63**, 782 (1941).

[93] Kindler, Hedemann, and Scharfe, *Ann.*, **560**, 215 (1948).

[94] Horning and Reisner, *J. Am. Chem. Soc.*, **71**, 1036 (1949).

[95] Horning and Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948).

[96] Legerlotz, Ger. pat. 522,790 [*C. A.*, **28**, 2723 (1934)].

[97] Brown, Bryan, and Enos, *J. Org. Chem.*, **11**, 384 (1946).

[98] Bruckner and von Fodor, *Ber.*, **76**, 466 (1943).

[99] Fischer and Baer, *Ber.*, **65**, 345 (1932).

[100] Freudenberg, Dürr, and Hochstetter, *Ber.*, **61**, 1735 (1928).

[101] Verkade, Cohen, and Vroege, *Rec. trav. chim.*, **59**, 1123 (1940).

[102] Verkade, Tollenaar, and Posthumus, *Rec. trav. chim.*, **61**, 373 (1942).

[103] Cavallito and Buck, *J. Am. Chem. Soc.*, **65**, 2140 (1943).

[104] McPhee, U. S. pat. 2,503,285 [*C. A.*, **44**, 6885 (1950)].

[105] McPhee, U. S. pat. 2,505,645 [*C. A.*, **44**, 6886 (1950)].

[106] Fodor and Kovacs, *J. Am. Chem. Soc.*, **71**, 1045 (1949).

[107] Gardner, Wenis, and Lee, *J. Org. Chem.*, **15**, 841 (1950).

[108] Clarke and Robertson, *J. Chem. Soc.*, **1949**, 302.

[109] Baxter, Ramage, and Timson, *J. Chem. Soc.*, **1949**, S 30.

[110] Kovacs and Horvath, *J. Org. Chem.*, **14**, 306 (1949).

[111] Foster, Howell, and Robertson, *J. Chem. Soc.*, **1939**, 930.

[112] Clarke, Glaser, and Robertson, *J. Chem. Soc.*, **1948**, 2260.

[113] Bruckner, Fodor, Kovacs, and Kiss, *J. Am. Chem. Soc.*, **70**, 2697 (1948).

[114] R. Simonoff, unpublished work.

[115] Heinzelmann, Aspergren, and Hunter, *J. Org. Chem.*, **14**, 907 (1949).

[116] Karrer and Ruttner, *Helv. Chim. Acta*, **33**, 812 (1950).

[117] Corwin and Damerel, *J. Am. Chem. Soc.*, **65**, 1974 (1943).

[118] Meyer, Hobby, and Chaffee, *Science*, **97**, 205 (1943).

[119] Cavallito and Harley, *J. Org. Chem.*, **15**, 815 (1950).

[120] Hardegger, El Heweicki, and Robinet, *Helv. Chim. Acta*, **31**, 439 (1948).

[121] Bowman, *Nature*, **162**, 111 (1948).

[122] Atherton, Openshaw, and Todd, *J. Chem. Soc.*, **1945**, 382.

[123] Atherton and Todd, *J. Chem. Soc.*, **1947**, 674.

[124] Atherton, Bergel, Cohen, Haworth, Openshaw, and Todd, Brit. pat. 593,480 [*C. A.*, **42**, 2281 (1948)].

[125] Fischer and Waibel, *Ann.*, **512**, 195 (1934).

[126] Bergmann, Zervas, and Ross, *J. Biol. Chem.*, **111**, 245 (1935).

[127] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, **115**, 593 (1936).

[128] Bergmann, Zervas, Fruton, Schneider, and Schleich, *J. Biol. Chem.*, **109**, 325 (1935).

[129] Prelog and Wieland, *Helv. Chim. Acta*, **29**, 1128 (1946).

[130] Bergmann and Ross, *J. Am. Chem. Soc.*, **58**, 1503 (1936).

[131] Bergmann, *Science*, **79**, 439 (1934).

[132] Bergmann, Zervas, and Rinke, *Z. physiol. Chem.*, **224**, 40 (1934).

[133] Bergmann, Zervas, Rinke, and Schleich, *Z. physiol. Chem.*, **224**, 26 (1934).

[134] Bergmann and Fruton, *J. Biol. Chem.*, **118**, 405 (1937).

[135] Bergmann, Zervas, Salzman, and Schleich, *Z. physiol. Chem.*, **224**, 17 (1934).

[136] Schott, Larkin, Rockland, and Dunn, *J. Org. Chem.*, **12**, 494 (1947).

[137] Chow, M. S. thesis, University of Maryland, 1950.

[138] Karrer and Heynemann, *Helv. Chim. Acta*, **31**, 398 (1948).

[139] Harris and Work, *Nature*, **161**, 804 (1948).

[140] Synge, *Biochem. J.*, **42**, 99 (1948).

[141] May and Mosettig, *J. Org. Chem.*, **15**, 890 (1950).

[142] Neuberger and Pitt Rivers, *J. Chem. Soc.*, **1939**, 122.

[143] Mattocks and Hartung, *J. Biol. Chem.*, **165**, 501 (1946).

[144] N. Levin, private communication.

[145] McMillan and Albertson, *J. Am. Chem. Soc.*, **70**, 3778 (1948).

[146] Simonoff and Hartung, *J. Am. Pharm. Assoc.*, **35**, 306 (1946).

[147] R. Baltzly, private communication; cf. ref. 59.

[148] Stolz and Flaecher, Ger. pat. 527,620 [*Frdl.*, **17**, 2513 (1932)]; Brit. pat. 318,488 [*C. A.*, **24**, 2240 (1930)].

[149] Baltzly and Buck, *J. Am. Chem. Soc.*, **62**, 164 (1940).

[150] Stolz, Hallensleben, and Kross, Ger. pat. 526,087 [*Frdl.*, **17**, 463 (1932)].

[151] Fosdick, Fancher, and Uhrbach, *J. Am. Chem. Soc.*, **68**, 840 (1946).

[152] Stolz and Bottcher, Ger. pat. 524,717 [*Frdl.*, **17**, 2515 (1932)].

[153] Aeschlimann and Stempel, U. S. pat. 2,512,732 [*C. A.*, **44**, 8961 (1950)].

[154] U. S. Dept. of Commerce, Office of Technical Services, PB **981**, 71 (1945).

[155] Eisleb, *Ber.*, **74**, 1447 (1941).

[156] U. S. Dept. of Commerce, Office of Technical Services, PB **981**, 94 (1945).

[157] Grewe, Mondon, and Nolte, *Ann.*, **564**, 161 (1949).

[158] Bockmuhl, Ehrhart, and Stein, Ger. pat. 600,771 [*C. A.*, **28**, 7430 (1934)].

[159] Bergmann, Zervas, and Overhoff, *Z. physiol. Chem.*, **224**, 52 (1934).

[160] Bergmann, Zervas, Rinke, and Schleich, *Z. physiol. Chem.*, **224**, 33 (1934).

[161] Priestly and Moness, *J. Org. Chem.*, **5**, 355 (1940).

[162] Stocken, *J. Chem. Soc.*, **1947**, 592.

[163] Sus, *Ann.*, **559**, 92 (1948).

[164] Hegedus, *Helv. Chim. Acta*, **31**, 737 (1948).

[165] Plentl, *J. Biol. Chem.*, **178**, 44 (1949).

CHAPTER 6

THE NITROSATION OF ALIPHATIC CARBON ATOMS

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CONTENTS

NATURE OF THE REACTION

The nitrosation reaction consists in the replacement of a hydrogen atom by the nitroso group, with the formation of a nitroso or oximino derivative. (Oximes formed by nitrosation reactions have often been called isonitroso compounds. Since isonitroso compounds are identical with oximes produced by other methods, the use of the dual terminology is gradually being discontinued.) With few exceptions, the replacement of hydrogen on an aliphatic carbon atom requires the presence of electron-attracting groups adjacent to the carbon to be nitrosated. Acyl, aroyl, carbonyl, carboxyl, carbalkoxyl, nitro, cyano, imino, and aryl groups may serve as activators, but they vary greatly in their capacity to promote nitrosation. Thus, monoketones are readily converted into α-oximino ketones, whereas monoesters containing no other activating groups do not undergo the reaction.

Victor Meyer discovered the reaction in 1873–1874, when he found that careful acidification of an alkaline solution of a nitroparaffin and an alkali nitrite converts a primary nitroparaffin into a nitrolic acid [1] and a secondary nitroparaffin into a pseudonitrole.[2,3] He subsequently

$$RCH_2NO_2 \xrightarrow{HNO_2} \underset{\substack{\| \\ NOH}}{RCNO_2}$$

$$R_2CHNO_2 \xrightarrow{HNO_2} \underset{\substack{| \\ NO}}{R_2CNO_2}$$
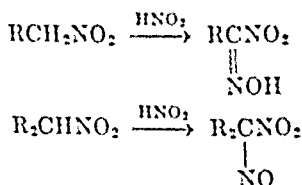
extended the reaction to β-keto esters by preparing ethyl α-oximino-acetoacetate from ethyl acetoacetate.[4,5]

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{HNO_2} \underset{\substack{\| \\ NOH}}{CH_3COCCO_2C_2H_5}$$
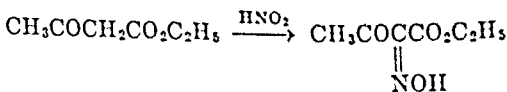
When a methyl or methylene group is nitrosated, the nitroso intermediate usually rearranges rapidly to the oxime. (The isolation of

$$RCOCH_2R \rightarrow \underset{\substack{| \\ NO}}{RCOCHR} \rightarrow \underset{\substack{\| \\ NOH}}{RCOCR}$$

$$CH_2(CO_2R)_2 \rightarrow ONCH(CO_2R)_2 \rightarrow HON=C(CO_2R)_2$$
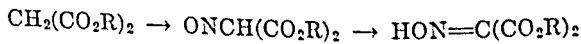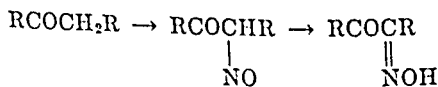
[1] Meyer, *Ber.*, 6, 1492 (1873).
[2] Meyer and Locher, *Ber.*, 7, 788 (1874).
[3] Meyer and Locher, *Ber.*, 7, 1506 (1874).
[4] Meyer, *Ber.*, 10, 2075 (1877).
[5] Meyer and Züblin, *Ber.*, 11, 320 (1878).

nitroso intermediates is reported on pp. 333, 338, and 339. The formation of stable nitroso derivatives of two β-diketones is discussed on p. 334.) Formation of an oximino structure frequently occurs even when it necessitates cleavage of the molecule at the carbon which has been nitrosated. Monosubstituted β-keto esters and malonic esters are thus converted into α-oximino esters. A mechanism for the base-catalyzed
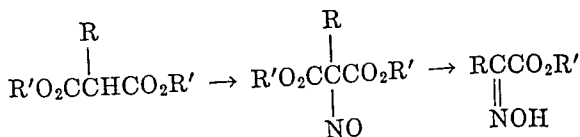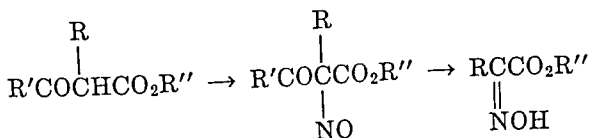
nitrosation and cleavage of a cyclic ketone has been proposed.[*,6] That
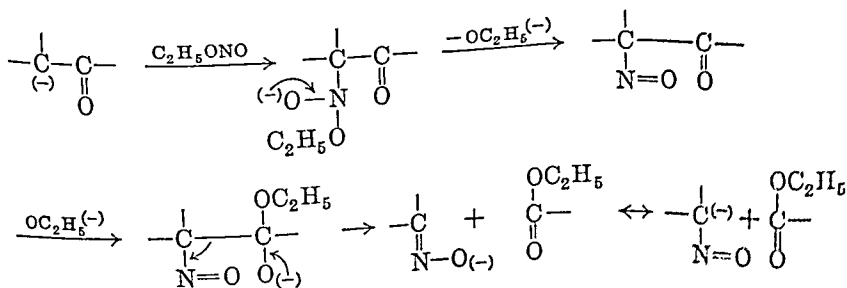
the cleavage of substituted β-keto esters and malonic esters upon reaction with ethyl nitrite and sodium ethoxide occurs by a similar mechanism is indicated by the isolation of ethyl benzoate and diethyl carbonate after the nitrosation of ethyl α-benzoylvalerate[7] and diethyl n-butylmalonate,[8] respectively. The cleavage of the nitroso derivative presumed to be formed from the β-keto ester may be represented by the

* In one of the contributing forms of the resonance hybrid, the nitrogen atom of an organic nitrite is considered to have but six electrons, thus making possible the electrophilic attack on the α-carbon atom.

6 Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).
6 Woodward and Doering, J. Am. Chem. Soc., 70, 4250 (1948).
7 Hauser and Reynolds, J. Am. Chem. Soc., 69, 1264 (1947).
8 Shivers and Hauser, J. Am. Chem. Soc.,

accompanying equation.[7]   The nitrosation of β-keto esters, malonic

$$C_6H_5COCCO_2C_2H_5 + NaOC_2H_5 \rightarrow C_6H_5C \longrightarrow CCO_2C_2H_5 \rightarrow$$

$$C_6H_5CO_2C_2H_5 + C_3H_7CCO_2C_2H_5$$
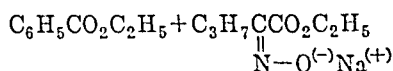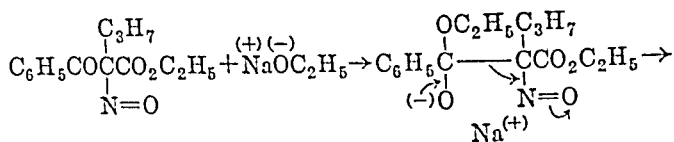
acids, and malonic esters in acid solution has been considered to involve reaction of the nitrosating agent with the enolic forms of these compounds.[9-14]

Nitrosations have been carried out with nitrous acid, nitrosyl chloride, nitrosylsulfuric acid, nitrous fumes, and esters of nitrous acid. Acid or base is usually added as catalyst with the last two reagents.

SCOPE AND LIMITATIONS

Since the principal governing factor in this reaction is the nature of the compound to be nitrosated, rather than the particular reagent used, the following discussion is based upon the types of compounds which undergo the reaction. There has been little study of side reactions; they are discussed briefly in the section on experimental conditions. The conversion of oximino products into the corresponding keto derivatives may be the most significant side reaction, but it is probably not serious if the usual nitrosation procedures are employed.

Ketones

A ketone group exerts a strong activating influence in the nitrosation of an adjacent carbon atom. The methylene group of a methyl alkyl ketone is attacked in preference to the methyl group. Diacetyl monoxime, an intermediate in the synthesis of dimethylglyoxime, is prepared in 69–74% yield by the action of ethyl nitrite and concentrated hydrochloric acid on methyl ethyl ketone.[15] (The effects of traces of water

[9] Barry and Hartung, *J. Org. Chem.*, **12**, 460 (1947).

[10] Bouveault and Locquin, *Bull. soc. chim. France*, [3] **31**, 1061 (1904).

[11] Meyer and Lenhardt, *Ann.*, **398**, 66 (1913).

[12] Onishchenko, *J. Gen. Chem.* (U.S.S.R.), **11**, 197 (1941) [*C. A.*, **35**, 7941 (1941)].

[13] Ritchie, *Advances in Enzymol.*, **7**, 95 (1947).

[14] Sidgwick, *The Organic Chemistry of Nitrogen*, revised by Taylor and Baker, p. 171, Oxford University Press, 1942.

[15] Semon and Damerell, *Org. Syntheses, Coll. Vol.* **2**, 204 (1943).

and of varying the amount of catalyst on the yield of diacetyl monoxime are discussed on p. 351.)   When 2,4-dinitrophenylacetone is treated

$$CH_3COCH_2CH_3 \xrightarrow[\text{(HCl)}]{C_2H_5ONO} CH_3COCCH_3$$
$$\overset{\|}{NOH}$$
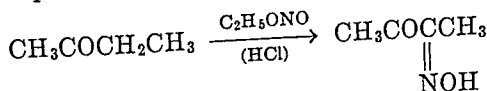
with isoamyl nitrite and hydrogen chloride in benzene, an 80% yield of 1-oximino-1-(2,4-dinitrophenyl)-2-propanone (I) is obtained.[16]   How-ever, isoamyl nitrite and sodium ethoxide in ethanol lead to the for-mation of 3-acetyl-6-nitrobenzisoxazole (II) and its decomposition product, 4-nitrosalicylonitrile (III). These compounds also result from the action of sodium ethoxide on the oxime I.
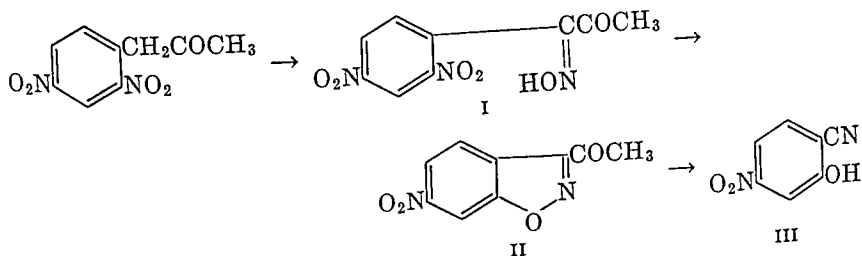
Dialkyl ketones with methylene groups in both α positions give rise to two isomeric oximino derivatives unless the alkyl groups differ con-siderably in length or unless one is branched. With alkyl groups of different lengths, nitrosation only of the shorter group is found.[17,18] With alkyl groups of similar size, branching of one of them leads to an oximino derivative formed by nitrosation of the unbranched chain.[17]

In a study of ketones containing tertiary carbon atoms adjacent to the carbonyl group, Aston and his co-workers [19,20] found that methyl ketones yield only tertiary nitroso derivatives. Both possible products were isolated from six ketones containing a secondary and a tertiary carbon atom adjacent to the carbonyl group. However, propyl iso-propyl ketone and butyl isopropyl ketone underwent only methylene nitrosation.[19]

Many methyl aryl ketones have been converted into their oximino derivatives, but the yields have not always been high. Acetophenols and propiophenols are usually nitrosated in lower yield than are the

[16] Borsche, *Ann.*, **390**, 1 (1912).
[17] Ponzio and DeGaspari, *J. prakt. Chem.*, [2] **58**, 392 (1898); *Gazz. chim. ital.*, **28**, 269 (1898).
[18] Ponzio and DeGaspari, *Gazz. chim. ital.*, **29**, 471 (1899).
[19] Aston and Mayberry, *J. Am. Chem. Soc.*, **57**, 1888 (1935).
[20] Aston, Menard, and Mayberry, *J. Am. Chem. Soc.*, **54**, 1530 (1932).

corresponding methoxy and halo compounds.[21-24]   This may be due to ring nitration (probably nitrosation followed by oxidation), since nitro-phenols are formed when phenols are allowed to react with amyl nitrite in ether for two or three days.[25]   Under most conditions acetophenone itself [21,26-32] gives lower yields of oximino derivative than does propio-phenone.[32-37]   Oximinomethyl 4-quinolyl ketone (IV) has been prepared in 60% yield by the action of amyl nitrite and sodium ethoxide on methyl 4-quinolyl ketone.[38]

$$
\underset{\text{N}}{\text{COCH}_3}\ \xrightarrow[\text{(NaOC}_2\text{H}_5)]{\text{C}_5\text{H}_{11}\text{ONO}}\ \underset{\text{N}}{\underset{\text{IV}}{\text{COCH=NOH}}}
$$
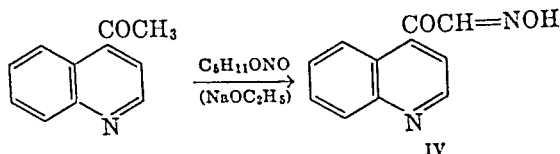
A number of substituted phenacyl chlorides have been converted in high yields into the corresponding arylglyoxylohydroxamyl chlorides (V).[39,40]   Another readily nitrosated group of alkyl aryl ketones is

$$
\text{ArCOCH}_2\text{Cl}\ \xrightarrow[\text{(HCl)}]{\text{C}_5\text{H}_9\text{ONO}}\ \underset{\underset{\text{V}}{\overset{\|}{\text{NOH}}}}{\text{ArCOCCl}}
$$
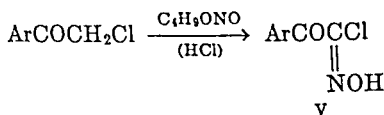
related to 1-indanone (α-hydrindone).[40a,41,42,43]   The action of amyl

[21] Edkins and Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936).

[22] Hartung, Munch, Miller, and Crossley, *J. Am. Chem. Soc.*, **53**, 4149 (1931).

[23] Pictet and Gams, *Ber.*, **42**, 2947 (1909).

[24] Zenitz and Hartung, *J. Org. Chem.*, **11**, 444 (1946).

[25] Ajello and Sigillò, *Gazz. chim. ital.*, **69**, 65 (1939).

[26] Bernton, *Arkiv Kemi, Mineral Geol.*, **7**, No. 13, 1 (1918) [*C. A.*, **14**, 2168 (1920)].

[27] Claisen, *Ber.*, **20**, 252 (1887).

[28] Claisen, *Ber.*, **20**, 656 (1887).

[29] Claisen, *Ber.*, **38**, 696 (1905).

[30] Claisen and Manasse, *Ber.*, **20**, 2194 (1887).

[31] Hartung, Munch, Deckert, and Crossley, *J. Am. Chem. Soc.*, **52**, 3317 (1930).

[32] Slater, *J. Chem. Soc.*, **117**, 587 (1920).

[33] Behr-Bregowski, *Ber.*, **30**, 1515 (1897).

[34] Claisen and Manasse, *Ber.*, **22**, 526 (1889).

[35] Edkins and Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 203 (1936).

[36] Hartung and Crossley, *Org. Syntheses, Coll. Vol. 2*, 363 (1943).

[37] Hartung and Munch, *J. Am. Chem. Soc.*, **51**, 2262 (1929).

[38] Rabe and Pasternack, *Ber.*, **46**, 1031 (1913).

[39] Levin and Hartung, *J. Org. Chem.*, **7**, 408 (1942).

[40] Levin and Hartung, *Org. Syntheses*, **24**, 25 (1944).

[40a] Kipping, *J. Chem. Soc.*, **65**, 492 (1894).

[41] Braun and Kirschbaum, *Ber.*, **46**, 3045 (1913).

[42] Gabriel and Stelzner, *Ber.*, **29**, 2604 (1896).

[43] Perkin and Robinson, *J. Chem. Soc.*, **91**, 1073 (1907).

nitrite and hydrochloric acid on 5,6-dimethoxy-1-indanone leads to the oximino derivative (VI) in almost quantitative yield.[43]
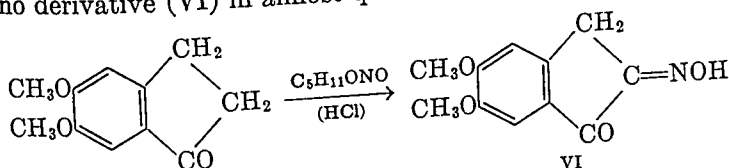
β-Diketones usually give good yields of oximino derivatives.[44-52] Nitroso intermediates (isolated as the dimers unless otherwise noted) may be obtained if the diketones in ether solution are treated with nitrous fumes.[50] Nitrosodibenzoylmethane (VII) has been prepared in this manner in 50–60% yield. Alkali, ammonia, or boiling ethanol converts this product into the corresponding oxime VIII. Further

$$C_6H_5COCH_2COC_6H_5 \xrightarrow{N_2O_3} \underset{\underset{\text{VII}}{\underset{|}{NO}}}{C_6H_5COCHCOC_6H_5} \xrightarrow{KOH} \underset{\underset{\text{VIII}}{\underset{||}{NOH}}}{C_6H_5COCCOC_6H_5}$$
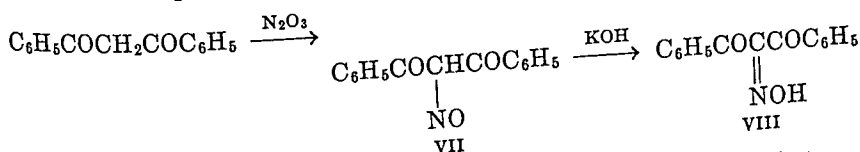
treatment of this oxime with nitrous fumes yields diphenyl triketone. This reagent effects, in one step, the quantitative conversion of p-nitrodibenzoylmethane into the corresponding triketone.[50] Methone (IX) has been nitrosated in 99% yield by potassium nitrite and hydrochloric acid.[45]
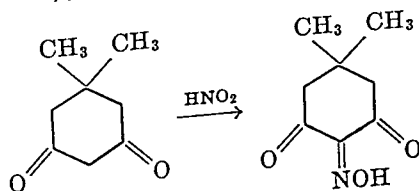
The nitrosation of 1,3-indanedione to the 2-oxime [53, 54] is of interest as a potential route to ninhydrin. Unfortunately, all attempts to hy-

[44] Ceresole, Ber., **17**, 814 (1884).
[45] Haas, J. Chem. Soc., **91**, 1437 (1907).
[46] Küster, Z. physiol. Chem., **155**, 157 (1926).
[47] Lifschitz, Ber., **46**, 3233 (1913).
[48] Neufville and Pechmann, Ber., **23**, 3378 (1890).
[49] Sachs and Herold, Ber., **40**, 2714 (1907).
[50] Wieland and Bloch, Ber., **37**, 1524 (1904).
[51] Wolff, Bock, Lorentz, and Trappe, Ann., **325**, 134 (1902).
[52] Zanetti, Gazz. chim. ital., **23**, 303 (1893).
[53] Teeters and Shriner, J. Am. Chem. Soc., **55**, 3026 (1933).
[54] Wislicenus, Ann., **246**, 353 (1888).

drolyze the nitrosation product were unsuccessful.[53] This stability towards hydrolysis has been attributed to the presence of a nitroso group rather than an oximino group in the 2 position.[55] The nitrosation product is oxidized to 2-nitro-1,3-indanedione by nitric acid and even by nitrous acid, which usually converts oximes to ketones. 2-Nitro-1,3-indanedione is reduced to the nitrosation product by formic acid. Another nitroso compound which does not rearrange to the oximino form in aqueous acid is the 4,9-dinitroso derivative obtained in 89% yield by the action of nitrous acid on 3,5,8,10-tetraketo-3,4,5,8,9,10-hexahydropyrene.[56]

Cyclic ketones appear to be preferentially nitrosated at a tertiary carbon atom. Baeyer converted menthone into nitrosomenthone (X) in 40% yield by means of ethyl nitrite and acetyl chloride [57] and into β,ζ-dimethyl-ϵ-oximinocaprylic acid (XI) in 60% yield by means of ethyl nitrite and hydrochloric acid.[58] However, other workers have
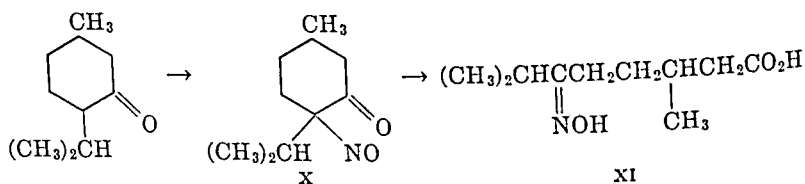
reported that the conversion of menthone into this oximino acid is poorly effected by amyl nitrite and hydrogen chloride but is accomplished in 68% yield by amyl nitrite and sodium ethoxide.[59] The nitrosation of pulegone (XII) is interesting in that it yields a derivative of isopulegone (XIII).[59] The base-catalyzed isomerization of pulegone to isopulegone apparently is sufficiently rapid for nitrosation to occur at the
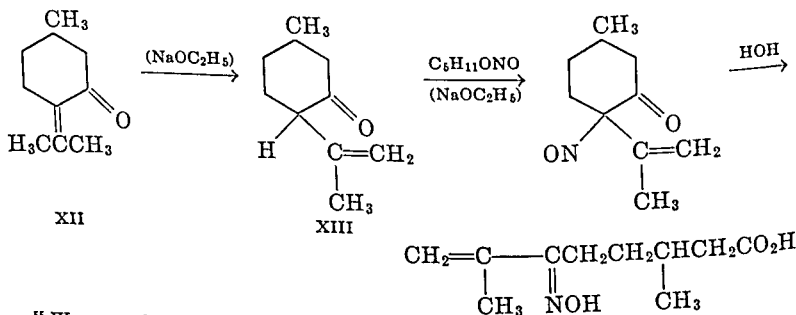
[55] Wanag and Lode, *Ber.*, **72**, 49 (1939).
[56] Vollmann, Becker, Corell, and Streeck, *Ann.*, **531**, 85 (1937).
[57] Baeyer, *Ber.*, **28**, 1586 (1895).
[58] Baeyer and Manasse, *Ber.*, **27**, 1912 (1894).
[59] Clarke, Lapworth, and Wechsler, *J. Chem. Soc.*, **93**, 30 (1908).

newly formed tertiary carbon rather than at the α-methylene group.[59a] A key N-Acetyl-10-oximinodihydrohomomeroquinene ethyl ester (XV), a key intermediate in the synthesis of quinine, is prepared in 68% yield by the nitrosation of cis-N-acetyl-7-keto-8-methyldecahydroisoquinoline (XIV).[6] An exception to the usual nitrosation of the tertiary carbon
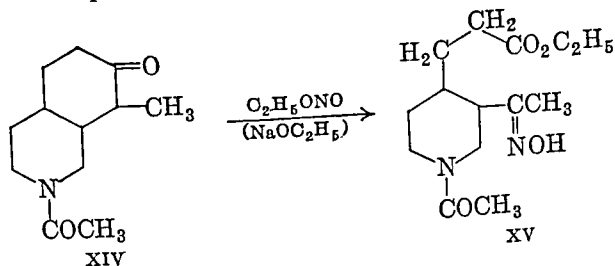
of cyclic ketones is observed in the reaction of (−)-epicamphor (XVI), which yields (−)-3-oximinoepicamphor (XVII) on treatment with amyl nitrite and sodamide in ether.[60] However, the tertiary carbon in this ketone is at the bridgehead of a fused ring system.
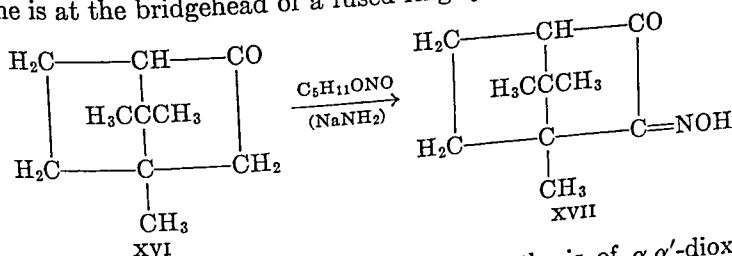
There have been several reports of the synthesis of α,α'-dioximino ketones by the nitrosation of monoketones.[61-65] (The synthesis of dioximinoacetone from acetonedicarboxylic acid and the failure to prepare ethyl α,α'dioximinoacetonedicarboxylate from ethyl acetonedicarboxylate are discussed below.) The isolation of α,α'-dioximinotropinone (XVIII) from the nitrosation of tropinone was useful in the proof of structure of tropinone, for it indicated that the carbonyl group was located between two methylene groups.[65] The use of amyl nitrite and hydrogen chloride in glacial acetic acid led to this dioxime in 90% yield. The same conditions have been used to convert 2,2,6-trimethyl-

[59a] Similarly, treatment of pulegone with hydroxylamine hydrochloride and excess potassium hydroxide yields the oxime of isopulegone. Wallach, *Ann.*, 365, 240 (1909).
[60] Bredt and Perkin, *J. Chem. Soc.*, 103, 2210 (1913).
[61] Borsche, *Wallach Fest.*, 1909, 301 [*Chem. Zentr.*, 1909, II, 1549].
[62] Harries and Groschuff, *Ann.*, 417, 181 (1918).
[63] Kötz, Nussbaum, and Takens. *J. prakt. Chem.*, [2] 90, 357 (1914).
[64] Wieland, *Ber.*, 37, 1145 (1904).
[65] Willstätter, *Ber.*, 30, 2698 (1897).

4-piperidone (vinyldiacetonamine) into its dioximino derivative XIX in 60% yield.[62]

$$
\begin{array}{l}
\text{H}_2\text{C—CH——C=NOH} \\
\quad\quad\quad | \quad\quad\quad | \\
\quad\quad\quad \text{NCH}_3 \quad \text{C=O} \\
\quad\quad\quad | \quad\quad\quad | \\
\text{H}_2\text{C—CH——C=NOH}
\end{array}
\qquad
\begin{array}{c}
\text{O} \\
\text{HON} \diagdown \quad \diagup \text{NOH} \\
\text{H}_3\text{C} \quad\quad (\text{CH}_3)_2 \\
\text{N} \\
\text{H}
\end{array}
$$
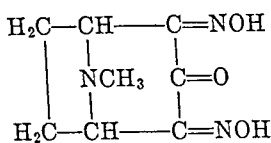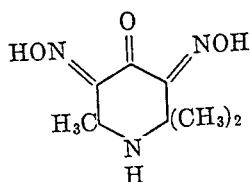
<div align="center">XVIII   XIX</div>

The activating effect of an ammono-ketone (ketimino) group is illustrated by the reaction of 2-methyl-3,3-dimethylpseudoindole (XX) with sodium nitrite and acetic acid.[66] The conversion of 1,3,3-trimethyl-
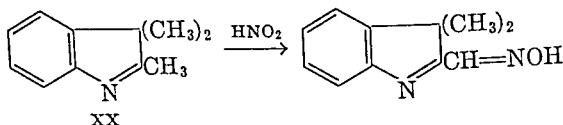
<div align="center">XX</div>

2-methylenedihydroindole (XXI) into the aldoxime XXII in 96% yield [67] may be considered as proceeding by way of the quaternary salt XXIII which has the structure of an ammono-ketone.

<div align="center">XXI   XXII   ClO$_4$(−)   XXIII</div>
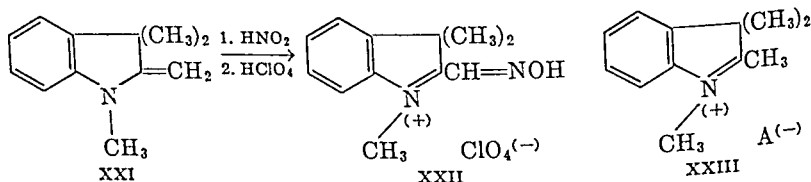
β-Keto Acids, Esters, and Related Compounds

The nitrosation of unsubstituted β-keto esters yields α-oximino-β-keto esters, whereas α-substituted β-keto esters are converted into α-oximino esters.[67a] If the β-keto ester is first hydrolyzed to the β-keto acid,

$$
\text{RCOCH}_2\text{CO}_2\text{R}' \rightarrow \text{RCOC CO}_2\text{R}'
$$
$$
\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad \underset{\text{NOH}}{\overset{\|}{}}
$$

$$
\begin{array}{c}
\text{R}'' \\
| \\
\text{RCOCHCO}_2\text{R}' \rightarrow \text{R}''\text{C CO}_2\text{R}' \\
\quad\quad\quad\quad\quad\quad \underset{\text{NOH}}{\overset{\|}{}}
\end{array}
$$
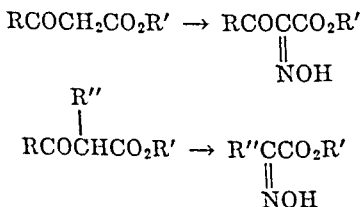
[61] Plancher and Bettinelli, *Gazz. chim. ital.*, **29**, 113 (1899).
[62] Kuhn, Winterstein, and Balser, *Ber.*, **63**, 3182 (1930).
[67a] The one exception to this generalization is the reaction between unsubstituted aceto-acetic esters and nitrosylsulfuric acid in sulfuric acid, which leads to oximinonacetic esters in good yield. Bouveault and Wahl, *Bull. soc. chim. France*, [3] **31**, 675 (1904).

treatment with nitrite yields an α-oximino ketone.[5, 68] This reaction has been developed into a general method for the synthesis of α-oximino ketones.[69, 70]   It permits the preparation of 3-oximino-2-pentanone (XXIV) from ethyl α-ethylacetoacetate in 94% yield.[71] α-Oximino

$$\underset{\text{CH}_3\text{COCHCO}_2\text{C}_2\text{H}_5}{\overset{\overset{\text{CH}_2\text{CH}_3}{|}}{}} \xrightarrow{\text{KOH}} \underset{\text{CH}_3\text{COCHCO}_2\text{H}}{\overset{\overset{\text{CH}_2\text{CH}_3}{|}}{}} \xrightarrow{\text{HNO}_2} \underset{\underset{\text{XXIV}}{\overset{||}{\text{NOH}}}}{\text{CH}_3\text{COCCH}_2\text{CH}_3}$$
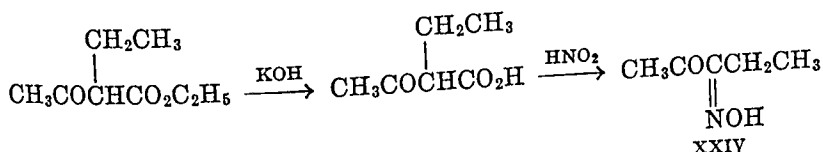
ketones are obtained from β-keto acids even when there is no substituent in the α position.   Thus, dioximinoacetone (XXV) is prepared in 51% yield by the action of nitrous acid on acetonedicarboxylic acid.[72-75]

$$\text{HO}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{H} \xrightarrow{\text{HNO}_2} \underset{\text{XXV}}{\text{HON}=\text{CHCOCH}=\text{NOH}}$$
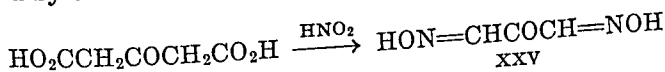
The nitrosation proceeds very rapidly, evolution of carbon dioxide occurring immediately upon the addition of nitrite.   Although 1,2-cyclo-hexanedione monoxime (XXVI) and its derivatives can be prepared by direct nitrosation of the corresponding monoketones, they are also available from the nitrosation of 2-carbethoxycyclohexanones.[76,77,78]
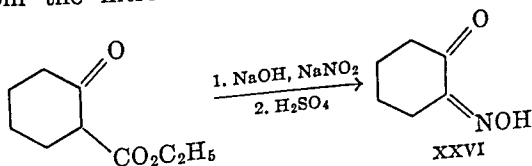
It should be noted that the success of this reaction depends on the careful exclusion of air from the reaction mixture during saponification.[76]
   The few reports dealing with β-imino acids and esters indicate that these compounds resemble β-keto acids and esters in their behavior

[68] Meyer and Züblin, *Ber.*, **11**, 692 (1878).
[69] Bouveault and Locquin, *Bull. soc. chim. France*, [3] **31**, 1164 (1904).
[70] Locquin, *Bull. soc. chim. France*, [3] **31**, 1159 (1905).
[71] Diels and Plaut, *Ber.*, **38**, 1919 (1905).
[72] Geissman, Schlatter, and Webb, *J. Org. Chem.*, **11**, 737 (1946).
[73] Koessler and Hanke, *J. Am. Chem. Soc.*, **40**, 1717 (1918).
[74] Mann and Pope, *Proc. Roy. Soc. London*, 107A, 84 (1925).
[75] Pechmann and Wehsarg, *Ber.*, **19**, 2465 (1886).
[76] Geissman and Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
[77] Jaeger and Bijkerk, *Proc. Acad. Sci. Amsterdam*, 40, 12 (1937) [*C. A.*, **31**, 4960 (1937)].
[78] Jaeger and van Dijk, *Proc. Acad. Sci. Amsterdam*, 39, 384 (1936) [*C. A.*, **30**, 6341 (1936)].

towards nitrosating agents.[79, 80, 81]   Ethyl α-cyano-β-imino-γ-oximino-butyrate (XXVIII) is produced by the action of nitrous acid on mono-ethyl α-cyano-β-iminoglutarate (XXVII).[79]

$$\underset{\substack{\text{NH} \quad \text{CN} \\ \textbf{XXVII}}}{HO_2CCH_2C\text{---}CHCO_2C_2H_5} \xrightarrow{HNO_2} \underset{\substack{\text{NOH} \; \text{NH} \; \text{CN} \\ \textbf{XXVIII}}}{CH\text{---}C\text{---}CHCO_2C_2H_5}$$
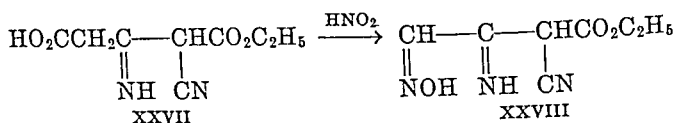
Benzoylacetimido ethyl ether (XXIX) is reported to yield its oximino derivative (XXX) when treated with amyl nitrite and hydrogen chloride.[26]   However, potassium nitrite and sulfuric acid lead to the formation of ethyl α-oximinobenzoylacetate (XXXI).

$$\underset{\substack{\text{NOH} \; \text{NH} \\ \textbf{XXX}}}{C_6H_5COC\text{---}COC_2H_5} \xleftarrow[\text{(HCl)}]{C_5H_{11}ONO} \underset{\substack{\text{NH} \\ \textbf{XXIX}}}{C_6H_5COCH_2COC_2H_5} \xrightarrow[H_2SO_4]{KNO_2}$$

$$\underset{\substack{\text{NOH} \\ \textbf{XXXI}}}{C_6H_5COCCO_2C_2H_5}$$
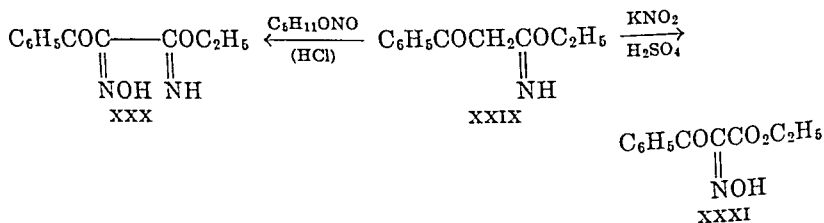
Schmidt and his co-workers [82–85] carried out the nitrosation of α-mono-alkyl β-keto esters with nitrous fumes in the absence of solvent and were able to isolate the intermediate monomeric nitroso esters, which were unstable blue or blue-green oils. On standing several days the nitroso

$$\underset{}{RCOCHCO_2R''} \xrightarrow{N_2O_3} \underset{\substack{\text{NO}}}{R'CHCO_2R''}$$
$$\overset{\substack{R' \\ |}}{}$$
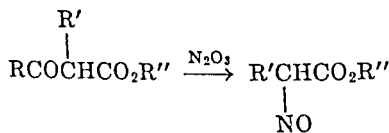
esters underwent both dimerization and rearrangement to the oxime. A trace of alkali brought about very rapid change to the oxime. With this nitrosation technique, it was found that the ease of cleavage of acyl groups decreased in the order: —CHO, —COCH₃, —COC₆H₅.[82]

Cyclic β-keto esters are usually cleaved to α-oximino diesters by nitrosation in the presence of alkali alkoxides. 2-Carbethoxy-4-methyl-

[79] Baron, Remfry, and Thorpe, J. Chem. Soc., 85, 1738 (1904).
[80] Euler and Euler, Ber., 37, 47 (1904).
[81] Knorr, Ber., 17, 1635 (1884).
[82] Schmidt and Dieterle, Ann., 377, 30 (1910).
[83] Schmidt and Haid, Ann., 377, 23 (1910).
[84] Schmidt and Widmann, Ber., 42, 498 (1909).
[85] Schmidt and Widmann, Ber., 42, 1886 (1909).

cyclohexanone is converted into diethyl α-oximino-γ-methyladipate in 25–30% yield by the action of nitrous fumes and sodium ethoxide, but almost twice this yield results from the use of ethyl nitrite and sodium ethoxide.[86] With 2-carbethoxycyclopentanone (XXXII), ethyl nitrite and sodium ethoxide lead to a 60% yield of diethyl α-oximinoadipate (XXXIII), whereas ethyl nitrite and acetyl chloride in the absence of solvent permit the isolation of the cyclic nitroso derivative (XXXIV) in 60–80% yield.[87] The nitroso intermediate can be cleaved to the oxime in nearly quantitative yield by the action of sodium ethoxide.

$$C_2H_5O_2CCH_2CH_2CH_2\underset{\underset{NOH}{\|}}{C}CO_2C_2H_5$$

XXXIII
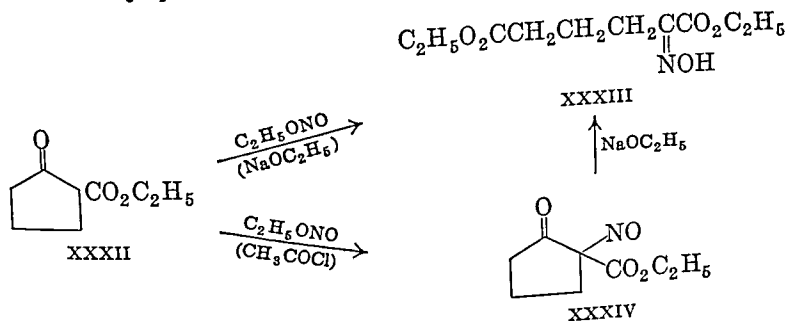
Bouveault and Locquin [10, 88–91] employed nitrosylsulfuric acid in concentrated sulfuric acid as a reagent for the conversion of α-monoalkyl β-keto esters into α-oximino esters (65–93% yield). Hamlin and Hartung [92] introduced a convenient modification of this procedure in which n-butyl nitrite and 85% sulfuric acid are used as the reagent combination. α-Oximino-δ-chloro-γ-valerolactone (XXXVI), which is used in the synthesis of hydroxyproline, is prepared from α-neopentyl δ-chloro-γ-valerolactone (XXXV) by Bouveault's method (67% yield).[93] The reaction of the lactone XXXV with sodium nitrite and dilute sulfuric acid takes an anomalous course, however, since the oxime acetate XXXVII is obtained (81% yield).[94] α-Oximino-γ-butyrolactone,

[86] Dieckmann and Groeneveld, *Ber.*, 33, 595 (1900).
[87] Dieckmann, *Ber.*, 33, 579 (1900).
[88] Bouveault and Locquin, *Compt. rend.*, 135, 179 (1902).
[89] Bouveault and Locquin, *Bull. soc. chim. France*, [3] 31, 1049 (1904).
[90] Bouveault and Locquin, *Bull. soc. chim. France*, [3] 31, 1055 (1904).
[91] Locquin, *Bull. soc. chim. France*, [3] 35, 962 (1906).
[92] Hamlin and Hartung, *J. Biol. Chem.*, 145, 349 (1942).
[93] McIlwain and Richardson, *Biochem. J.*, 33, 45 (1939).
[94] Feofilaktov and Onishchenko, *Compt. rend. acad. sci. U.R.S.S.*, 20, 133 (1939) [*C. A.*, 33, 1725 (1939)].

$$\underset{\text{XXXVII}}{\overset{\overset{\displaystyle\text{NOCOCH}_3}{\|}}{\text{ClCH}_2\text{CHCH}_2\text{CCO}}} \quad \xleftarrow{\text{HNO}_2} \quad \underset{\text{XXXV}}{\overset{\overset{\displaystyle\text{COCH}_3}{|}}{\text{ClCH}_2\text{CHCH}_2\text{CHCO}}} \quad \xrightarrow{\text{NO}_2\text{SO}_3\text{H}}$$

$$\underset{\text{XXXVI}}{\overset{\overset{\displaystyle\text{NOH}}{\|}}{\text{ClCH}_2\text{CHCH}_2\text{CCO}}}$$
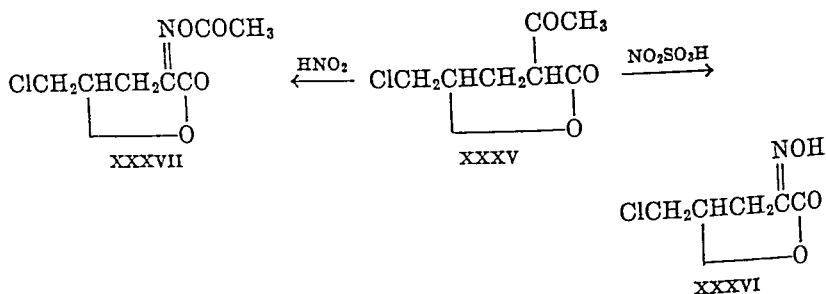
an intermediate in a synthesis of methionine, is prepared in 85–91% yield from α-acetyl-γ-butyrolactone, ethyl nitrite, and hydrogen chloride.[95]

Diethyl acetonedicarboxylate (XXXVIII) is easily converted to its monoximino derivative by an alkyl nitrite and hydrogen chloride,[96,97] but isoxazole formation occurs when dinitrosation is attempted.[97] The second mole of nitrite obviously serves as an oxidizing agent rather than as a nitrosating agent. The oxime XXXIX and the isoxazole XL have been used in the preparation of β-hydroxyglutamic acid [96] and β,γ-dihydroxyglutamic acid,[98] respectively.

$$\text{HO}_2\text{CCH}_2\underset{\overset{|}{\text{OH}}}{\text{CH}}-\underset{\overset{|}{\text{NH}_2}}{\text{CHCO}_2}\text{H}$$

$$\Bigg\uparrow \begin{array}{l}\text{1. H}_2\text{(Pd, Pt)} \\ \text{2. HOH}\end{array}$$

$$\text{C}_2\text{H}_5\text{O}_2\text{CCH}_2\text{COC}\overset{\overset{\displaystyle\|}{\text{NOH}}}{\text{CCO}_2}\text{C}_2\text{H}_5$$

XXXIX

$$\underset{\text{XXXVIII}}{\text{C}_2\text{H}_5\text{O}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5} \quad \xrightarrow[\text{(HCl)}]{1\ \text{C}_5\text{H}_{11}\text{ONO}} \quad$$

$$\xrightarrow[\underset{2\ \text{C}_5\text{H}_{11}\text{ONO}}{\text{(HCl)}}]{}$$

$$\underset{\text{XL}}{\text{C}_2\text{H}_5\text{O}_2\text{CC}\!=\!\overset{\overset{\displaystyle\text{OH}}{|}}{\text{C}}-\underset{\text{N}}{\overset{\text{O}}{\underset{|}{\text{C}}}}\text{CCO}_2\text{C}_2\text{H}_5}$$

$$\Bigg\downarrow \begin{array}{l}\text{1. H}_2\text{(Ni)} \\ \text{2. HOH}\end{array}$$

$$\text{HO}_2\text{CCH}-\underset{\overset{|}{\text{OH}}}{\text{CH}}-\underset{\overset{|}{\text{NH}_2}}{\text{CHCO}_2}\text{H}$$
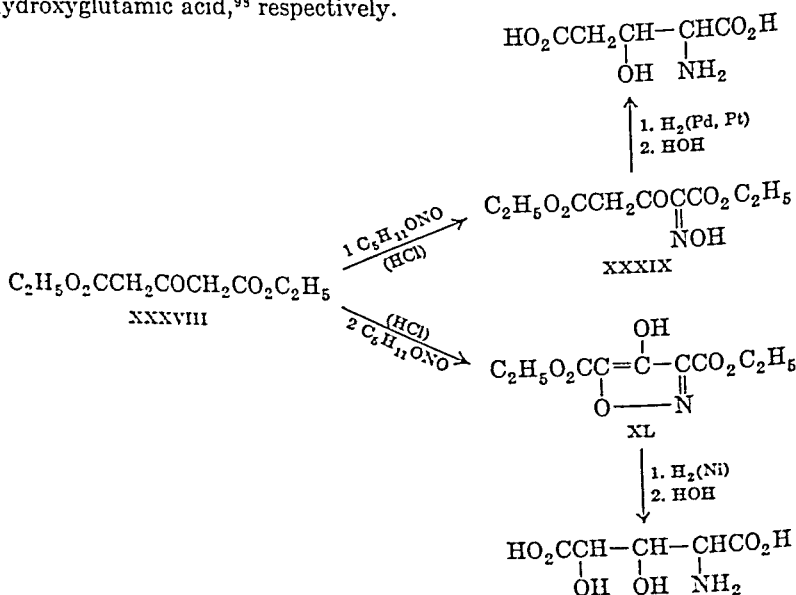
[*] Snyder, Andreen, Cannon, and Peters, J. Am. Chem. Soc., 64, 2083 (1942).
[96] Harington and Randall, Biochem. J., 25, 1917 (1931).
[97] Pechmann, Ber., 24, 860 (1891).
[98] Touster and Carter, J. Am. Chem. Soc., 73, 54 (1951).

α-Methyltetronic acid (XLI) gives either of two products with nitrous fumes, depending upon the solvent employed.[99] A 57% yield of the nitroso derivative XLII is obtained with glacial acetic acid, whereas a 90% yield of α-oximinopropionylglycolic acid (XLIII) results with water as solvent. It has been reported that other α-substituted tetronic
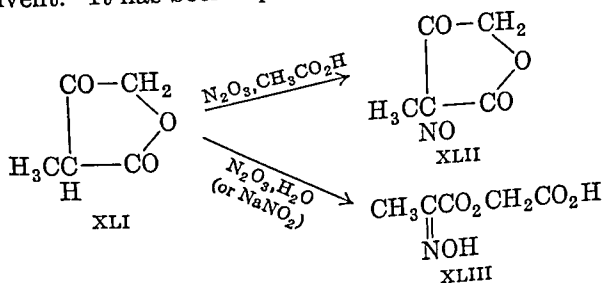
acids may suffer loss of the α substituent.[100] Sodium nitrite converted α-ethyltetronic acid (XLIV) into α-oximinotetronic acid (65% yield) and acetaldehyde. No explanation was offered for the unusual course of this reaction.
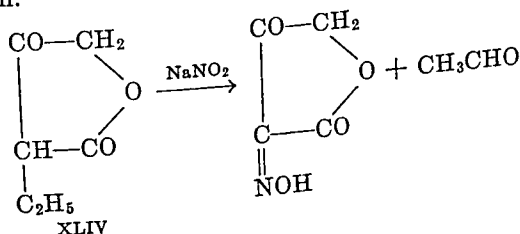
Malonic Acids, Esters, and Amides

Alkylmalonic acids are decarboxylated during nitrosation.[9, 12, 101, 102]

$$RCH(CO_2H)_2 \xrightarrow[\text{(HCl)}]{R'ONO} RCCO_2H$$
$$\overset{\parallel}{NOH}$$
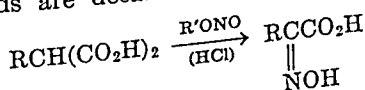
Recent studies have shown that excellent yields of α-oximino acids can be obtained by this reaction.[9, 12, 101] The action of isopropyl nitrite and hydrogen chloride on 3,4-methylenedioxybenzylmalonic acid furnishes an 85–90% yield of α-oximino-β-(3,4-methylenedioxyphenyl)propionic acid, an intermediate in a synthesis of 3,4-dihydroxyphenylalanine.[101]

[99] Wolff, Ann., 288, 1 (1895).
[100] Wolff and Herold, Ann., 399, 311 (1913).
[101] Barry, Mattocks, and Hartung. J. Am. Chem. Soc., 70, 693 (1948).
[102] Kletz and Lapworth, J. Chem. Soc., 107, 1254 (1915).

Diethyl oximinomalonate has been prepared from diethyl malonate in good yield under a variety of experimental conditions.[103-113]   Alkyl nitrites, with sodium ethoxide as catalyst, are very effective in converting substituted malonic esters into α-oximino esters.[8, 9, 114]   Ethyl α-oximino-

$$RCH(CO_2R')_2 \xrightarrow[\text{(NaOR'')}]{\text{R''ONO}} \underset{\underset{NOH}{\parallel}}{RCCO_2R'}$$
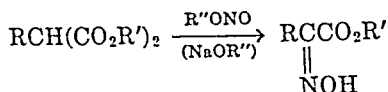
caproate, ethyl α-oximino-β-phenylpropionate, and ethyl α-oximino-δ-diethylaminovalerate have been prepared in this manner in yields of 80%, 92%, and 94%, respectively.[8]

A number of amides and anilides of malonic acid have been converted into their oximino derivatives.[115, 116, 117]   Quantitative yields of oximes were often obtained with nitrosyl chloride as nitrosating agent.[117]

Arylacetic Acids and Esters

Only a small number of arylacetic acids and esters have been subjected to nitrosation.   Ethyl phenylacetate and ethyl p-bromophenylacetate have been converted into their oximino derivatives in good yield by ethyl nitrite and potassium ethoxide.[118]

$$C_6H_5CH_2CO_2C_2H_5 \xrightarrow[\text{(KOC_2H_5)}]{\text{C_2H_5ONO}} \underset{\underset{NOH}{\parallel}}{C_6H_5CCO_2C_2H_5}$$
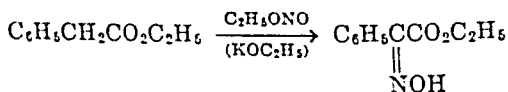
Results with nitrophenylacetic acids and esters have not been uniform. Although a few compounds of this type have yielded oximino derivatives

upon treatment with amyl nitrite and a basic or acidic catalyst,[119,120] others have shown little reactivity towards nitrous acid.[121] The unusual importance of the nitrosating agent employed is further indicated by the lack of reaction between "2,4-dinitrophenylacetic ester" and isoamyl nitrite and hydrogen chloride in benzene.[16] Sodium methoxide catalysis, on the other hand, promotes the conversion of methyl 2,4-dinitrophenylacetate into 3-carbomethoxy-6-nitrobenzisoxazole in 85% yield.[16]

Nitriles

Nitrous acid effects the conversion of methyl and ethyl cyanoacetates into their oximino derivatives in 90% yield,[122-125] but the combination of amyl nitrite and sodium ethoxide leads to poor yields of these products.[123] The nitrosation of substituted cyanoacetic esters, like that of

$$NCCH_2CO_2R \xrightarrow{HNO_2} NCCCO_2R$$
$$\underset{NOH}{\overset{\|}{}}$$
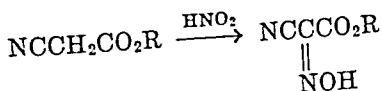
substituted malonic esters, effects decarbalkoxylation, producing the corresponding α-oximinonitriles.[126] Oximinoarylacetonitriles have been

$$RCHCN \xrightarrow[\text{(KOC}_2\text{H}_5)]{\text{R'ONO}} RCCN$$
$$\underset{CO_2C_2H_5}{\overset{|}{}} \qquad \underset{NOH}{\overset{\|}{}}$$
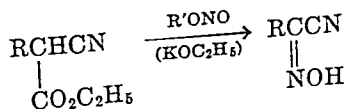
prepared directly by the action of alkyl nitrites and sodium ethoxide on arylacetonitriles.[127,128] Nitrous acid converts cyanoacetamides into their oximino derivatives.[122,129]

The synthesis of oximinomalononitrile (XLV) has been attempted by the nitrosation of malononitrile. Amyl nitrite and sodium ethoxide gave a high yield of a compound assigned the structure α-oximino-β-hydroxy-

[119] Borsche, Ber., 42, 3596 (1909).
[120] Gabriel and Meyer, Ber., 14, 823 (1881).
[121] Parkes and Aldis, J. Chem. Soc., 1938, 1841.
[122] Conrad and Schulze, Ber., 42, 735 (1909).
[123] Muller, Ann. chim. phys., [7] 1, 463 (1894).
[124] Nef, Ann., 280, 331 (1894).
[125] Fields, Walz, and Rothchild, J. Am. Chem. Soc., 73, 1000 (1951).
[126] Walker, J. Chem. Soc., 125, 1622 (1924).
[127] Frost, Ann., 250, 163 (1889).
[128] Zimmermann, J. prakt. Chem., [2] 66, 353 (1902).
[129] Merck, Ger. pat. 227,390 [Brit. C. A., 100(i), 166 (1911)].

$$\underset{\substack{| \\ \text{NH}_2 \ \text{NOH} \\ \text{XLVI}}}{\overset{\substack{\text{OH} \\ |}}{\text{C}_2\text{H}_5\text{OC}\!\!-\!\!-\!\!-\!\!\text{CCN}}} \xleftarrow[\text{(NaOC}_2\text{H}_5)]{\text{C}_5\text{H}_{11}\text{ONO}} \text{CH}_2(\text{CN})_2 \xrightarrow{\text{HNO}_2} \underset{\text{XLV}}{\text{HON}\!=\!\text{C(CN)}_2}$$
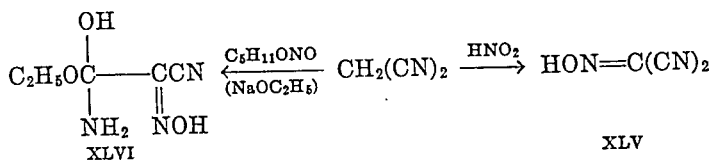
β-Iminopropionitriles have been found to react with nitrosating agents.[132, 133] Amyl nitrite in ether converts β-imino-β-phenylpropionitrile (benzoacetodinitrile, XLVII) into the ammonium salt of α-oximino-β-nitrosimino-β-phenylpropionitrile (XLVIII).[*, 132] The ammonia necessary for the formation of this compound undoubtedly comes from decomposition of the original nitrile, since oximinobenzoylacetonitrile (XLIX) can also be isolated.

$$\underset{\substack{\| \\ \text{NH} \\ \text{XLVII}}}{\text{C}_6\text{H}_5\text{CCH}_2\text{CN}} \xrightarrow{\text{C}_5\text{H}_{11}\text{ONO}} \underset{\substack{\| \quad\quad \| \\ \text{NNO} \ \text{NONH}_4 \\ \text{XLVIII}}}{\text{C}_6\text{H}_5\text{C}\!\!-\!\!-\!\!-\!\!\text{CCN}} + \underset{\substack{\| \\ \text{NOH} \\ \text{XLIX}}}{\text{C}_6\text{H}_5\text{COCCN}}$$
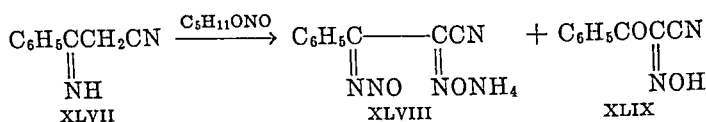
Only a small amount of dioximinosuccinonitrile is formed by the action of two equivalents of amyl nitrite and potassium ethoxide on succinonitrile.[119]

Nitro Compounds

Nitrosation converts primary nitroparaffins into nitrolic acids [1, 134] and secondary nitroparaffins into pseudonitroles.[2, 3, 134] These reactions are the basis of Meyer's "red, white, and blue" test for nitro compounds.[135] Alkaline solutions of nitrolic acids are blood-red in color, whereas pseudonitroles give the blue solutions expected of nitroso compounds. Tertiary nitroparaffins do not undergo nitrosation. Ethyl nitrolic acid (L) [136] (acetonitrolic acid) and butyl pseudonitrole (LI) [3] have been prepared in 82% and 78% yield, respectively. The reaction is carried

[130] Diels and Borgwardt, *Ber.*, **54**, 1334 (1921).

[131] Longo, *Gazz. chim. ital.*, **61**, 578 (1931).

[132] Lublin, *Ber.*, **37**, 3467 (1904).

[133] Meyer, *J. prakt. Chem.*, [2] **52**, 108 (1895).

* A similar compound is reported to be one of the products formed from amyl nitrite and ethyl β-aminocrotonate (ethyl β-iminobutyrate) (see ref. 80).

[134] Meyer and Locher, *Ber.*, **7**, 670 (1874).

[135] Meyer and Locher, *Ber.*, **7**, 1510 (1874).

[136] Wieland, *Ann.*, **353**, 82 (1907).

$$\overset{\overset{\textstyle \|}{NOH}}{\underset{L}{}}$$

$$\underset{\text{LI}}{CH_3CH_2\overset{\overset{\textstyle NO_2}{|}}{C}HCH_3 \xrightarrow{HNO_2} CH_3CH_2\overset{\overset{\textstyle NO_2}{|}}{\underset{\underset{\textstyle NO}{|}}{C}}CH_3}$$
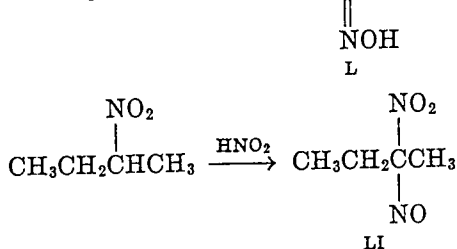
out by the addition of potassium nitrite and dilute sulfuric acid to an alkaline solution of the nitro compound. When 1,3-dihydroxy-2-nitropropane (LII) is treated in this manner, hydroxyethyl nitrolic acid (LIII) and formaldehyde are formed.[137] The cleavage of the hydroxymethyl group may be similar to that which occurs when other tertiary nitroso intermediates undergo cleavage with rearrangement to the oximes, or it may result from an alkali-catalyzed retrograde aldol condensation prior to nitrosation.

$$\underset{\text{LII}}{HOCH_2\overset{\overset{\textstyle NO_2}{|}}{C}HCH_2OH} \xrightarrow[\underset{-CH_2O}{}]{} \underset{}{HOCH_2\overset{\overset{\textstyle NO_2}{|}}{\underset{\underset{\textstyle NO}{|}}{C}}CH_2OH} \xrightarrow{-CH_2O} HOCH_2CH_2NO_2 \longrightarrow \underset{\text{LIII}}{HOCH_2\overset{\overset{\textstyle CNO_2}{\underset{\underset{\textstyle NOH}{\|}}{}}}{}}$$
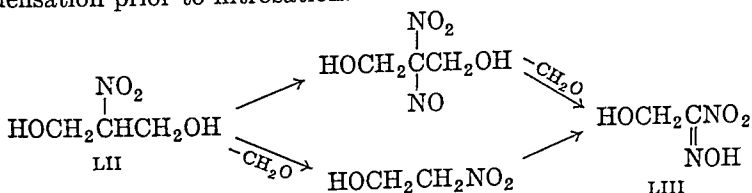
In accordance with the general reactivity of alkyl groups *ortho* and *para* to a nitro group, *o*- and *p*-nitrotoluene, nitro-*p*-xylene, *o*-nitroethylbenzene, *m,p'*-dinitrodiphenylmethane, and phenyl *p*-nitrobenzyl ether are nitrosated by amyl nitrite and an alkoxide.[138–141] Although there is not much published information about this reaction, it has been stated that the oxime of *o*-nitrobenzaldehyde (LIV) can be prepared with little difficulty if alcohol-free sodium ethoxide is used as catalyst.[141]

LIV
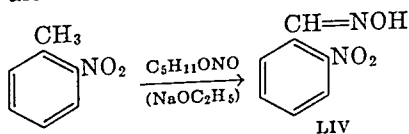
[137] Earl, Ellsworth, Jones, and Kenner, *J. Chem. Soc.*, **1928**, 2697.
[138] Angeli and Angelico, *Atti accad. nazl. Lincei*, [5] 8, II, 28 (1899) [*Chem. Zentr.*, **1899**, II, 371].
[139] Farbwerke vorm Meister, Lucius, and Brüning, Ger. pat. 107,095 [*Chem. Zentr.*, **1900**, I, 886].
[140] Farbwerke vorm Meister, Lucius, and Brüning, Ger. pat. 109,663 [*Chem. Zentr.*, **1900**, II, 458].
[141] Lapworth, *J. Chem. Soc.*, **79**, 1274 (1901).

However, there is disagreement about the necessity of using alcohol-free sodium ethoxide in this reaction.[139]

The activating effect of the nitro group described in the preceding paragraphs is to be contrasted with the opposite effect which this group sometimes exerts. Thus, although ethyl phenylacetate has been nitrosated successfully,[116] methyl 2,4-dinitrophenylacetate is reported to undergo nitrosation only in an alkaline medium.[16, 121] p-Nitrobenzylmalonic acid and ethyl p-nitrobenzylacetoacetate are reported not to undergo nitrosation.[142]

Hydrocarbons

As would be expected from the general reactivity of its methylene group, cyclopentadiene (LV) can be nitrosated in 70–90% yield.[143]

$$
\begin{array}{ccc}
HC\!\!=\!\!CH & & HC\!\!=\!\!CH \\
| \quad \diagdown CH_2 & \xrightarrow[(NaOC_2H_5)]{C_2H_5ONO} & | \quad \diagdown C\!\!=\!\!NOH \\
HC\!\!=\!\!CH & & HC\!\!=\!\!CH \\
LV & & (as\ a\ dimer)
\end{array}
$$
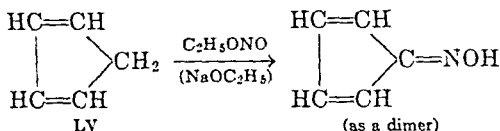
Lynn and his co-workers[144] found that sunlight catalyzes a reaction between hydrocarbons and nitrosyl chloride. Heptane was converted into the oxime of di-n-propyl ketone,[145] and toluene gave benzaldoxime in almost quantitative yield based on the nitrosyl chloride.[146]

SYNTHETIC APPLICATIONS

α-Oximino Acids and Esters

α-Oximino acids and esters are most frequently prepared by the nitrosation of substituted β-keto esters, malonic acids, and malonic esters. The other methods available for the preparation of these oximes are (1) reaction of an α-keto acid or ester with hydroxylamine,[142, 147, 148, 149] (2) reaction of an α-halo acid with hydroxylamine,[150] (3) reaction of an α-halo ester with sodium nitrite,[92, 151, 152, 153] and (4) formation, oxidation,

[142] Mattocks and Hartung. J. Am. Pharm. Assoc., 35, 18 (1946).
[143] Thiele. Ber., 33, 669 (1900).
[144] Lynn. J. Am. Chem. Soc., 41, 368 (1919).
[145] Lynn and Hilton. J. Am. Chem. Soc., 44, 645 (1922).
[146] Lynn and Arkley. J. Am. Chem. Soc., 45, 1045 (1923).
[16] Meyer and Janny. Ber., 15, 1525 (1882).
[147] Puitti. Gazz. chim. ital., 17, 519 (1887).
[148] Erlenmeyer. Ann., 271, 167 (1892).
[92] Hantzsch and Wild. Ann., 289, 285 (1896).
[151] Lepercq. Bull. soc. chim. France, [3] 9, 630 (1893).
[152] Lepercq. Bull. soc. chim. France, [3] 11, 295 (1894).
[153] Lepercq. Bull. soc. chim. France, [3] 11, 886 (1894).

and hydrolysis of an α-hydroxylaminonitrile.[154]   The usefulness of reaction 1 is limited by the comparative unavailability of α-keto acids, whereas reactions 2, 3, and 4 require relatively long reaction times.

$$(1) \qquad RCOCO_2H \xrightarrow{\ NH_2OH\ } \underset{\underset{NOH}{\|}}{R}CCO_2H$$

$$(2) \qquad \underset{\underset{X}{|}}{R}CHCO_2H \xrightarrow{\ HN_2OH\ } \underset{\underset{NOH}{\|}}{R}CCO_2H$$

$$(3) \qquad \underset{\underset{X}{|}}{R}CHCO_2R' \xrightarrow{\ NaNO_2\ } \underset{\underset{NOH}{\|}}{R}CCO_2R'$$

$$(4) \qquad \underset{\underset{NOH}{\|}}{R}CH \xrightarrow{\ HCN\ } \underset{\underset{HNOH}{|}}{R}CHCN \xrightarrow{\ H_2SO_4\ } \underset{\underset{NOH}{\|}}{R}CCONH_2 \xrightarrow{\ HOH\ } \underset{\underset{NOH}{\|}}{R}CCO_2H$$
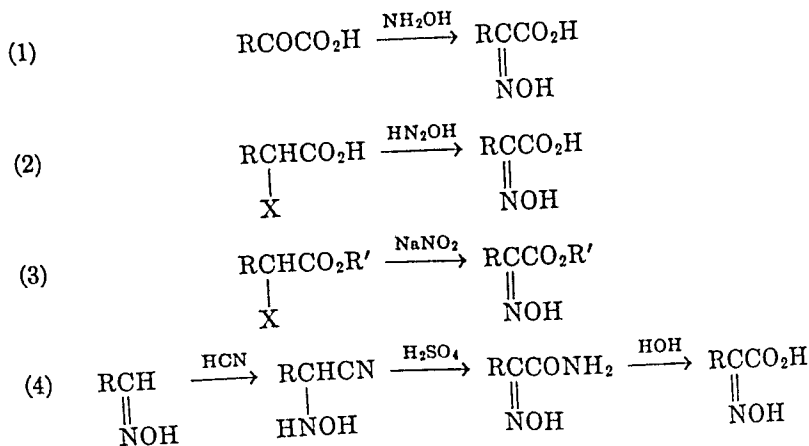
α-Oximino acids and esters prepared by nitrosation reactions have been used extensively in the synthesis of the corresponding α-amino acids and esters. The α-amino acids which have been prepared in this manner are alanine,[92] α-amino-n-butyric acid,[92] α-amino-δ-diethyl-aminovaleric acid (ethyl ester),[8,155] 3,4-dihydroxyphenylalanine,[101] glutamic acid,[92,93] β-hydroxyglutamic acid,[96] isoleucine,[92,156] leucine,[12,92] lysine,[157,158] p-methoxyphenylalanine,[92] norleucine[92] (ethyl ester[8]), norvaline,[92] phenylalanine[12,92] (ethyl ester[8]), the α-amino-β-hydroxy-n-butyric acids,[159] and tyrosine.[92]   In recent years many α-amino acids have been prepared from substituted aminocyanoacetic and aminomalonic esters obtained from ethyl oximinocyanoacetate and diethyl oximinomalonate, respectively.[126,160]

α-Oximino esters also provide a route to α-keto acids and esters, since the oximino group can be replaced by a keto group by treatment with a nitrous acid derivative.[161-164]   Diethyl oxomalonate (LVI) is prepared from diethyl malonate in 74 to 76% yield without isolation of the

[154] Miller and Plöchl, *Ber.*, 26, 1545 (1893).
[155] Breslow, Walker, Yost, Shivers, and Hauser, *J. Am. Chem. Soc.*, 68, 101 (1946).
[156] Bouveault and Locquin, *Bull. soc. chim. France*, [3] 35, 965 (1906).
[157] Olynyk, Camp, Griffith, Woislowski, and Helmkamp, *J. Org. Chem.*, 13, 468 (1948).
[158] Borsook, Deasy, Haagen-Smit, Keighley, and Lowy, *J. Biol. Chem.*, 176, 1384 (1948).
[159] Adkins and Reeve, *J. Am. Chem. Soc.*, 60, 1328 (1938).
[160] Albertson, *J. Am. Chem. Soc.*, 68, 450 (1946).
[161] Bouveault and Locquin, *Bull. soc. chim. France*, [3] 31, 1142 (1904).
[162] Kondo, *Biochem. Z.*, 38, 408 (1912).
[163] Locquin, *Bull. soc. chim. France*, [3] 31, 1147 (1904).
[164] Sen, *Biochem. Z.*, 143, 197 (1923).

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{N_2O_3} CO(CO_2C_2H_5)_2$$
$$\text{LVI}$$
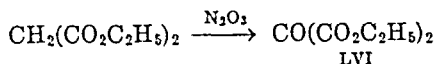
intermediate oximino ester.[165] The same reaction can be accomplished more satisfactorily by means of the commercially available nitrogen dioxide.[166]

The use of α-benzyloximino acid chlorides in the synthesis of peptides is described on p. 271.

α-Oximino Ketones

α-Oximino ketones, prepared readily by the nitrosation of ketones and β-keto acids, have served in the synthesis of a large number of α-diketones, α-dioximes, α-diamines, α-amino alcohols, α-amino ketones, and heterocyclic compounds. The diketones have been prepared in high yield by treatment of the α-oximino ketones with dilute mineral acid [167] or with a nitrous acid derivative.[50,168,169] There is a report of the direct conversion, in high yield, of a β-diketone (p-nitrodibenzoylmethane) into the corresponding triketone by means of nitrous fumes.[50] Knorr's method [170,171,172] for the synthesis of pyrroles involves the reduction of an α-oximino ketone to an α-amino ketone, which, usually without isolation, is condensed with a ketone to form a substituted pyrrole. Ethyl acetoacetate is converted into 2,4-dimethyl-3,5-dicarbethoxypyrrole (LVII) by this procedure.[173] The amino ketones derived from α-oximino ketones
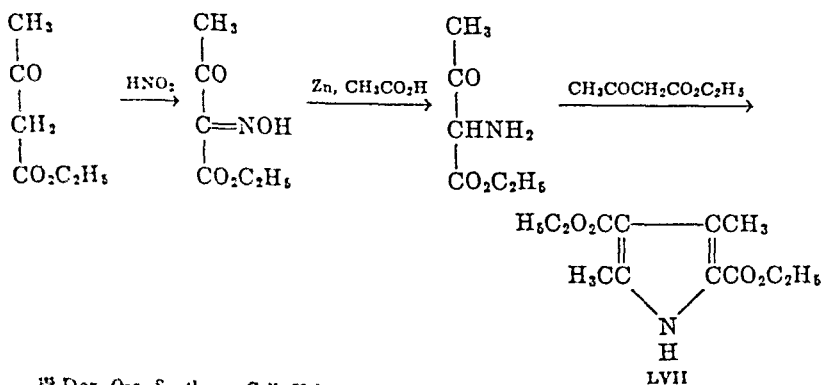
[165] Dox, Org. Syntheses, Coll. Vol. 1, 266 (1941).
[166] Riebsomer and Irvine, Org. Syntheses, 25, 34 (1945).
[167] Kolb, Ann., 291, 280 (1896).
[168] Bouveault and Locquin, Bull. soc. chim. France, [3] 31, 1169 (1904).
[169] Locquin, Bull. soc. chim. France, [3] 31, 1173 (1904).
[170] Knorr, Ann. 236, 317 (1886).
[171] Oehmi, Tsuda, and Ikuma, Ber., 68, 1551 (1935).
[172] Oehmi, Tsuda, and Ikuma, Ber., 68, 1710 (1935).
[173] Fischer, Org. Syntheses, Coll. Vol. 2, 202 (1943).

have served also in the synthesis of imidazolones (LVIII) and thiol-imidazoles (LIX).[33, 73, 174-177] The catalytic reduction of α-oximino ketones

$$
\begin{array}{ccc}
\text{RC—NH} & & \text{RC—NH} \\
\| \quad\quad > \text{CO} & \xleftarrow{\text{KCNO}} \text{RCOCH}_2\text{NH}_2 \cdot \text{HCl} \xrightarrow{\text{KCNS}} & \| \quad\quad > \text{CSH} \\
\text{HC—NH} & & \text{HC—N} \\
\quad\text{LVIII} & & \quad\text{LIX}
\end{array}
$$
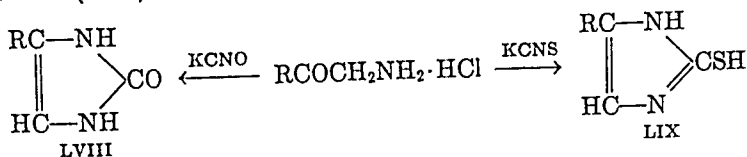
leads to α-amino ketones, α-amino alcohols, α-hydroxy oximes, or pyrazines, depending upon the experimental conditions.[93, 178] For example, the hydrogenation of ethyl α-oximinoacetoacetate (LX) over Raney nickel at 120 atm. yields, after oxidation of the product by air, 2,5-dimethyl-3,6-dicarbethoxypyrazine (LXI); hydrogenation at 320 atm.

$$
\xrightarrow[\text{2. O}_2\text{(air)}]{\underline{\text{1. Condensation}}}
\begin{array}{c}
\text{H}_3\text{C} \quad \text{N} \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{C}_2\text{H}_5\text{O}_2\text{C} \quad \text{N} \quad \text{CH}_3 \\
\text{LXI}
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_3\text{COCCO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{H}_2} \text{CH}_3\text{COCHCO}_2\text{C}_2\text{H}_5 \\
\quad\quad \| \quad\quad\quad\quad\quad\quad\quad\quad | \\
\quad\quad \text{NOH} \quad\quad\quad\quad\quad\quad\quad \text{NH}_2 \\
\quad\quad \text{LX} \quad\quad\quad\quad\quad\quad\quad\quad \xrightarrow{\text{H}_2} \text{CH}_3\text{CH—CHCO}_2\text{C}_2\text{H}_5 \\
\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad | \quad\quad | \\
\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad \text{OH} \quad \text{NH}_2 \\
\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad \text{LXII}
\end{array}
$$
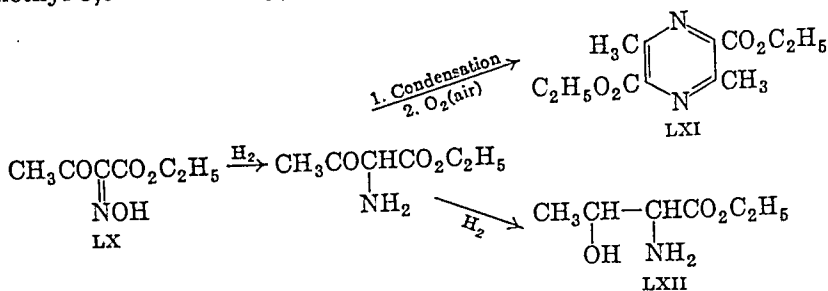
furnishes ethyl α-amino-β-hydroxy-n-butyrate (LXII).[159] Many of the α-oximino ketones obtained from aryl alkyl ketones have been reduced to amino alcohols that have pressor activity.[21, 22, 31, 35, 37, 179, 180, 181]

EXPERIMENTAL CONDITIONS AND PROCEDURES

Experimental Conditions

Since nitrous acid derivatives can convert oximes into ketones, the nitrosation of aliphatic carbon atoms is usually carried out with only a small excess of nitrosating agent * and at temperatures between 0 and

[174] Fox, Sargent, and Buchman, *J. Am. Chem. Soc.*, **67**, 496 (1945).
[175] Jackman, Klenk, Fishburn, Tullar, and Archer, *J. Am. Chem. Soc.*, **70**, 2884 (1948).
[176] Ochiai and Ikuma, *Ber.*, **69**, 1147 (1936).
[177] Wynn and Corwin, *J. Org. Chem.*, **15**, 203 (1950).
[178] Adkins and Shriner, in Gilman, *Organic Chemistry*, Vol. I, 2nd ed., p. 807, John Wiley & Sons, New York, 1943.
[179] Glynn and Linnell, *Quart. J. Pharm. Pharmacol.*, **5**, 491 (1932).
[180] Hartung, Munch, and Crossley, *J. Am. Chem. Soc.*, **57**, 1091 (1935).
[181] Machlis and Blanchard, *J. Am. Chem. Soc.*, **57**, 176 (1935).
* An interesting exception to this practice is the conversion of methylhydrastein into its oximino derivative in 80% yield by means of a twenty-two fold excess of ethyl nitrite (see ref. 239).

50°. It is customary to add one reactant in small portions to a stirred solution of the remaining reactants.

The isolation of products is largely dependent upon the solvent and reagents employed. Oximes are frequently purified by extraction into sodium carbonate or sodium hydroxide solution, provided they are stable under these conditions. Since heating of oximino derivatives may cause violent decomposition, care should be used in attempts to distill these compounds or to remove solvents by distillation (see page 354).

It is not always possible to make a rigorous differentiation among the various reagents employed in the nitrosation of aliphatic compounds because the effective nitrosating agent is often formed after the reactants have been brought together. For example, ethyl nitrite is the nitrosating agent when it is used with sodium ethoxide as catalyst, but with hydrogen chloride as catalyst the agent is believed to be nitrosyl chloride ("nascent nitrosyl chloride").[152] The following discussion is therefore based upon the reagents employed rather than on compounds believed to be formed in the reaction mixture.

The alkyl nitrites cause a marked fall in blood pressure by dilating the peripheral arteries. In large amounts they produce methemoglobinemia, resulting in cyanosis and asphyxia. Therefore, *alkyl nitrites, particularly methyl and ethyl nitrites, which are gases at room temperature, should be used with caution.*

1. Inorganic nitrite and acid. This combination possesses the advantage of avoiding the preliminary preparation of the nitrosating agent. It can be used with both water-soluble and water-insoluble compounds. The water-insoluble compounds have been nitrosated by employing glacial acetic acid as solvent and sodium nitrite dissolved in the minimum amount of water. Nitroparaffins are usually nitrosated by the addition of nitrite and mineral acid to an alkaline solution of the nitro compound.

2. Alkyl nitrite and an alkoxide. This effective combination is almost always used in ethanol solution. Only in the conversion of o- and p-nitrotoluene to the corresponding benzaldehyde oxime has alcohol-free alkoxide been said to be necessary,[141] but even in this case there is a conflicting report.[119] The claim[29] that the presence of a trace of water increases the yield of diacetylmonoxime from methyl ethyl ketone could not be confirmed.[152]

Ethyl nitrite nitrosates camphor more readily and in higher yield than does amyl nitrite.[144] Sidgwick[14] attributes to Slater[32] a report of

[152] Rheinboldt and Schmitz-Dumont, *Ann.*, **444**, 113 (1925).
[141] Semon and Damerell, *J. Am. Chem. Soc.*, **47**, 2033 (1925).
[119] Pope and Splittgerber, *Ber.*, **40**, 4313, footnote (1907).

the more rapid action of methyl and ethyl nitrites as compared to amyl nitrite; and, although no statement or experiment regarding this question appears in the paper by Slater, it is probably true that the lower homologs are more reactive. Probably a more important advantage of the use of one of the gaseous nitrites is that the alcohol (methanol or ethanol) formed in the reaction is both miscible with water and readily volatile, so that its presence does not complicate the isolation of the product. Gero and Seitchik [184a] recommend *n*-propyl nitrite as also having this advantage and as being preferred to methyl and ethyl nitrites because it can be handled as a liquid (b.p. 46–49°).

3. Alkyl nitrite and hydrogen chloride. This is the most widely used reagent combination. It has the advantage of yielding a reaction mixture which, by vacuum distillation, can be freed of reagents and at least one by-product, the alcohol formed from the nitrite. Ethanol and ether are used most frequently as solvents. A small amount of concentrated hydrochloric acid is often the source of the hydrogen chloride, but many nitrosations are carried out under anhydrous conditions. Slater [32] and Aston and Mayberry [19] found that water decreased the activity of the catalyst in ketone nitrosations, but Semon and Damerell [183] reported that a small amount of water had very little effect on the yield of diacetylmonoxime from methyl ethyl ketone. In a study of the nitrosation of a number of phenacyl chlorides, it was found necessary to add a trace of water to initiate the reaction of *p*-methoxyphenacyl chloride with isopropyl nitrite and hydrogen chloride.[39] With some ketones, maximum yields of their oximino derivatives depend upon the use of an optimum concentration of catalyst.[32, 183] Many nitrosations require continuous introduction of hydrogen chloride, but a trace suffices in the reaction between ethyl nitrite and α-acetyl-γ-butyrolactone.[95] Although the use of a large amount of hydrochloric acid has been reported to lead to nitrosochlorination,[27, 185] normally the use of an alkyl nitrite and hydrogen chloride is not complicated by this side reaction. Acetyl chloride can be used in place of hydrogen chloride.[19]

4. Nitrosation in concentrated sulfuric acid. Bouveault's method [10, 88–91] employing nitrosylsulfuric acid ("lead chamber crystals") in concentrated sulfuric acid for the nitrosation of α-substituted β-keto esters has been replaced by the more convenient method of Hartung,[9, 92] in which nitrosation is accomplished by *n*-butyl nitrite in 85% sulfuric acid. Its usefulness depends upon the stability of the compounds employed in the strong acid.[9]

[184a] Gero and Seitchik, private communication.
[185] Claisen and Manasse, *Ann.*, **274**, 95 (1893).

5. Nitrosyl chloride. The use of this reagent is attended with the disadvantage that nitrosochlorination as well as simple nitrosation may occur.[182, 186, 187]

6. Nitrous fumes. This reagent is seldom used at present for the nitrosation of aliphatic carbon atoms. It has had, however, extensive use in the preparation of N-nitroso-N-acetylarylamines.[187a] The fact that the reagent is a gas as well as a mixture of nitrogen oxides makes it difficult to employ it in a quantitative manner.

Experimental Procedures

The preparations of methyl nitrite,[36] ethyl nitrite,[15] and n-butyl nitrite [188] are described in *Organic Syntheses*. n-Butyl nitrite and, presumably, other organic nitrites decompose after several weeks at room temperature.

Directions for the preparation of oximinoacetone, diacetyl monoxime, 2-oximino-3-pentanone, and 2-oximino-3-hexanone are given by Fischer and Orth.[188a]

Detailed procedures for the preparation of diacetyl monoxime, α-oximinopropiophenone, and phenylglyoxylohydroxamyl chloride (ω-chloroisonitrosopropiophenone) from the corresponding ketones in yields of 69–74%, 65–68%, and 82–86%, respectively, are given in *Organic Syntheses*.[15, 36, 40] Alkyl nitrites and hydrogen chloride or hydrochloric acid are used to effect the nitrosations.

Dioximinoacetone from Acetonedicarboxylic Acid.[72] A solution of 150 g. of crude acetonedicarboxylic acid [188b] in 275 ml. of water is cooled in an ice-salt bath. A solution of 100 g. of sodium nitrite in 200 ml. of water is added slowly, with stirring, while the temperature of the reaction mixture is kept below 0°. The mixture is cooled to −5° and filtered immediately. The solid is washed with small portions of ice water. An additional amount is obtained by adding 200 ml. of cold 6 N nitric acid to the filtrate. The white product is washed with four small portions of ice water and dried over sulfuric acid in a vacuum desiccator. The product weighs 59 g. (51%) and decomposes at 133°.

[182] Demole, *Ann.*, **175**, 146 (1875).

[15] Rheinboldt and Schmitz-Dumont, *Ber.*, **61**, 32 (1928).

[187a] Bachmann and Hoffman, in Adams, *Organic Reactions*, Vol. II, p. 249, John Wiley & Sons, 1944.

[188] Noyes, *Org. Syntheses*, *Coll. Vol.* **2**, 108 (1943.)

[188a] H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. 1, pp. 408–410, Akad. Verlag, Leipzig, 1934.

[188b] Adams, Chiles, and Rassweiler, *Org. Syntheses*, *Coll. Vol.* **1**, 10 (1941). The crude acetonedicarboxylic acid contains sulfuric acid.

3-Oximino-5-ethoxy-2-pentanone from Ethyl α-2-Ethoxyethylaceto-acetate.[189] To 20 g. of 5% sodium hydroxide solution is added 78 g. of ethyl α-2-ethoxyethylacetoacetate, and the mixture is stirred for nine hours. Then 26.6 g. of solid sodium nitrite is added, and the orange solution is cooled in an ice bath while a solution of 30 ml. of concentrated sulfuric acid in 80 ml. of water is slowly added from a dropping funnel. The solution is allowed to stand overnight. It is then made alkaline with 10% sodium hydroxide solution and extracted with ether. The aqueous solution is acidified with sulfuric acid (saturation with carbon dioxide may be used), the product separating as a red-brown oil. The aqueous layer is extracted with ether, and the combined oil and extracts are washed free of acid, dried over sodium sulfate, and distilled. The yield of product boiling at 108–113°/2.3 mm. is 30 g. (49%). The freezing point of a redistilled sample (116–116.5°/1.4 mm.) is 29.5°.

Ethyl α-Oximinoacetoacetate from Ethyl Acetoacetate.[159] In a 5-l. three-necked flask fitted with a thermometer, a reflux condenser, and a mechanical stirrer are placed 730 ml. (750 g., 5.8 moles) of commercial ethyl acetoacetate and 840 ml. of glacial acetic acid. The flask is cooled in an ice-salt bath, and a solution of 450 g. of 95% sodium nitrite in a liter of water is added over a period of approximately one hour, the temperature being kept at 25°. Three liters of water is then added, and stirring is continued for two hours.

One quarter of the reaction mixture is placed in a 2-l. separatory funnel and shaken with 350 ml. of ether. The bottom aqueous layer is run off, and the next quarter of the reaction mixture is placed in the separatory funnel and extracted with the same ether. This is repeated until all is extracted. This cycle is repeated twice, using 200 ml. of ether each time. The ether extracts are combined, washed once with water, four times with sodium bicarbonate solution, and once more with water. The addition of sodium chloride is occasionally necessary to cause the layers to separate promptly. After drying the ether solution with sodium sulfate, the solvent is distilled on a steam bath at atmospheric pressure, and then for two hours at about 35 mm. The residue of brown, liquid, impure ethyl α-oximinoacetoacetate weighs 650–700 g.

The crude product is dissolved in toluene (120 ml. per 100 g. of crude material) and the solution is filtered. Cooling to −13° to −15° with stirring for one-half hour causes crystallization. The solid is filtered, washed with a little cold toluene, and air dried overnight. A yield of 550–600 g. (63%), m.p. 57.5–58°, is obtained. The addition of petroleum

[189] Tota and Elderfield, *J. Org. Chem.*, **7**, 317 (1942).

ether (b.p. 60–90°) to the toluene decreases the solubility of the product and permits an increased yield (75%).[190]

The once-crystallized material may be recrystallized from toluene, but 180 ml. of solvent should be used per 100 g. of oximino ester; the recovery of pure white product, m.p. 58–58.5°, is 90%. If the toluene mother liquor is distilled on a hot plate at atmospheric pressure, the oximino ester decomposes, sometimes violently. The mother liquor can be used for crystallizing the next batch of crude material, or most of the toluene can be distilled under reduced pressure on a steam bath and 50–60 g. more of the oximino ester, m.p. 56°, obtained on cooling.

α-Oximino-γ-butyrolactone from α-Acetyl-γ-butyrolactone.[95] To a cold (0° to −5°) solution of 256 g. (2 moles) of α-acetyl-γ-butyrolactone in 500 ml. of methanol is added 300 g. (4 moles) of ethyl nitrite.* The reaction flask is packed in ice and salt and allowed to stand for fifteen to twenty hours, during which time the ice melts and the temperature reaches that of the room. The mixture is cooled, and the crystalline solid is collected on a filter. The filtrate is concentrated under diminished pressure, and the dark-colored residue is heated on the steam bath with 100 ml. of n-butyl alcohol. The mixture is cooled and filtered. The two crops of crystals are combined, washed twice with 100-ml. portions of cold n-butyl alcohol and then with ether. The α-oximino-γ-butyrolactone weighs 196–209 g. (85–91%) and melts at 183–185° (lit. 192°).

α-Oximinocaproic Acid from Ethyl n-Butylacetoacetate.[9] In a 400-ml. beaker surrounded by an ice-salt bath is placed 30 g. of 85% sulfuric acid. Mechanical stirring is started (a four-blade paddle stirrer was found most efficient), and, when the temperature of the acid reaches −5° to 0°, 18.6 g. (0.1 mole) of ethyl n-butylacetoacetate is added slowly enough that no rise in temperature occurs. When this addition is complete, 11 g. (0.105 mole) of n-butyl nitrite is slowly added dropwise, with the temperature as near 0° as possible. Slow effervescence is observed, but, if the nitrite is added too rapidly, oxides of nitrogen are evolved. After all the nitrite has been added, small pieces of ice are added to dilute the acid. At this point a white, curdy precipitate of oximino ester appears. Cold water is then added, and the liquid is extracted with ether. The oximino compound is extracted from the ether by cold 10% sodium hydroxide solution. The red alkaline extract is heated on the steam bath for fifteen minutes, then cooled and acidified. The precipitated α-oximinocaproic acid is filtered, and the filtrate is

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[190] Albertson, Tullar, King, Fishburn, and Archer, *J. Am. Chem. Soc.*, **70**, 1150 (1948).

* Evidently the reaction is catalyzed by a trace of hydrogen chloride present in the ethyl nitrite, since with ethyl nitrite prepared from sulfuric acid the reaction proceeds very slowly unless a small amount of an acid is added.

extracted with ether. The product is recrystallized from petroleum ether and melts at 136° (dec.); the yield is 12.5 g. (86%).

By the same procedure, ethyl α-benzylacetoacetate is converted into α-oximino-β-phenylpropionic acid in 85% yield. No oxime could be obtained from ethyl 3,4-diethoxybenzylacetoacetate by this procedure.

Ethyl α-Oximinocaproate from Diethyl n-Butylmalonate.[8] Sixty-four and nine-tenths grams (0.3 mole) of diethyl n-butylmalonate is placed in a 500-ml. flask equipped with a mercury-sealed stirrer, dropping funnel, and an ice-water-cooled condenser carrying a drying tube. The flask is immersed in an ice bath, and 33.8 g. (0.4 mole) of ethyl nitrite * is added to the stirred solution, the temperature of which is maintained at about 0°. The mixture is then cooled to −10° in an ice-salt bath, and a solution of sodium ethoxide (prepared from 6.9 g. of sodium and 138 ml. of absolute ethanol) is added slowly with stirring. The flask is stoppered tightly and kept in a freezing unit of a refrigerator at −10° for twelve hours. The mixture is poured into an evaporating dish which is kept in a vacuum desiccator over concentrated sulfuric acid until the alcohol has evaporated. (The alcohol may be removed rapidly with equally good results by gently heating the mixture on a steam bath under reduced pressure.) To the residue is added an equal volume of ice water, and the aqueous solution is extracted with ether.† While it is cooled in an ice bath, the aqueous solution is acidified to pH 5 with cold concentrated hydrochloric acid. (During the neutralization, ice is added directly to the aqueous solution.) The α-oximino ester, which precipitates as a yellow oil, is taken up in ether, and the aqueous solution is extracted several times with ether. The combined ether extracts are dried over Drierite, and the solvent is distilled, leaving 42.8 g. (83%) of ethyl α-oximinocaproate as a light yellow solid, m.p. 49–53°. Recrystallization from petroleum ether (b.p. 30–60°) yields 41.4 g. (80%) of a white product melting at 53–55°.

By a similar procedure, diethyl benzylmalonate is converted into ethyl α-oximino-β-phenylpropionate in 92% yield.

* Purified commercial butyl nitrite gave quite impure ethyl α-oximinocaproate.

† From the ether solution, after drying and removing the solvent, there was obtained 9.4 g. (27%) of diethyl carbonate.

TABULAR SURVEY

The data in the tables cannot always be used to determine the superiority of a particular nitrosation procedure inasmuch as many preparations were not carried out with a view to obtaining maximum yields. Experimental procedures have been indicated by the following notations.

HNO_2 = sodium nitrite and mineral or acetic acid.

N_2O_3 = nitrous fumes evolved from a mixture of concentrated nitric acid and arsenic trioxide.

$NOCl$ = nitrosyl chloride.

NO_2SO_3H = nitrosylsulfuric acid in concentrated sulfuric acid.

C_4H_9ONO, 85% H_2SO_4 = n-butyl nitrite in 85% sulfuric acid.

RONO, HCl = alkyl nitrite * and hydrogen chloride. (Differentiation between anhydrous hydrogen chloride and concentrated aqueous hydrogen chloride has not been made unless the two reagents were compared under similar conditions.)

RONO, CH_3COCl = alkyl nitrite * and acetyl chloride.

RONO, MOR = alkyl nitrite * and an alkoxide.

HOH = hydrolysis.

Where more than one reference is given for a single entry, the yield reported is taken from the reference in italics.

Although many examples of the reaction are not listed in abstract journals, it is hoped that practically all those recorded in the literature prior to the January, 1950, issue of *Chemical Abstracts* † have been detected. A number of more recent examples are also included in the tables. The compounds are in general listed in order of increasing size and complexity, particularly as regards the group which is nitrosated. Methyl ketones therefore precede other dialkyl ketones, which are in turn followed by alicyclic ketones and then aryl alkyl ketones. In each of the tables, examples of the nitrosation of methyl groups precede examples of the nitrosation of methylene and methinyl groups.

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* Amyl nitrite and isoamyl nitrite are both listed as $C_5H_{11}ONO$ because commercial products may be mixtures of isomers.

† For the convenience of the reader, *Chemical Abstracts* references have been included for several foreign articles listed in this chapter. However, except for references 26, 235, 237, and 248, the original papers have been consulted.

TABLE I

KETONES

A. Dialkyl Monoketones

Starting Compound	Method	Products	Yield %	Reference
Acetone	N_2O_3	Acetylmethyl nitrolic acid *	23	191
	N_2O_3	Isonitrosodiacetone nitrate(?)	—	192
	HNO_2	Oximinoacetone	69	46
	CH_3ONO, HCl	Oximinoacetone	40	32
	$C_5H_{11}ONO$, HCl	Oximinoacetone	—	27
	NOCl	Oximinoacetone, chloroöximinoacetone, nitrosochlorination products of phorone	—	193
Methyl ethyl ketone	N_2O_3	Diacetyl monoxime	10	191
		Ethyl nitrolic acid	97	159
	CH_3ONO, HCl	Diacetyl monoxime	65, 69-74	183, 15
	C_2H_5ONO, HCl	Diacetyl monoxime	50-64 †	194, 195, 125, 197
	$C_5H_{11}ONO$, HCl	Diacetyl monoxime	62	198, 199
	$C_3H_{11}ONO$, HCl	Diacetyl monoxime	22	29
	$C_5H_{11}ONO$, $NaOC_2H_5$	Diacetyl monoxime	83 ‡	29
	$C_5H_{11}ONO$, NaOH	Diacetyl monoxime	51 †	200
	$C_5H_{11}ONO$	Diacetyl monoxime	—	183, 187, 193
	NOCl	Diacetyl monoxime	57	201
	NO_2SO_3H	Diacetyl monoxime	30-70	202
	NO_2SO_3H §	Diacetyl monoxime		
Methyl n-propyl ketone	$C_3H_{11}ONO$, HCl	3-Oximino-2-pentanone ‖	39	31
Methyl isopropyl ketone	C_2H_5ONO, HCl	3-Nitroso-3-methyl-2-butanone	24	19
	C_2H_5ONO, aq. HCl	3-Nitroso-3-methyl-2-butanone	43	29
	C_2H_5ONO, CH_3COCl	3-Nitroso-3-methyl-2-butanone	9	19
Acetopropyl alcohol	C_2H_5ONO, HCl	3-Oximino-5-pentanol-2-one	—	173
Methyl n-butyl ketone	$C_3H_{11}ONO$, HCl	3-Oximino-2-hexanone	45-64	203
Methyl 4-keto-2-pentenoate	C_2H_5ONO, HCl	Methyl 5-oximino-1-keto-2-pentenoate ¶	30-70	177
Mesityl oxide	$C_3H_{11}ONO$, $NaOC_2H_5$	1-Oximino-4-methyl-3-penten-2-one	40	31
Methyl n-hexyl ketone	$C_5H_{11}ONO$, HCl	3-Oximino-2-octanone	17	55, 204
Methyl cyclohexyl ketone	C_2H_5ONO, HCl	Methyl α-nitrosocyclohexyl ketone	13	19
	C_2H_5ONO, aq. HCl	Methyl α-nitrosocyclohexyl ketone		19

Ketone	Reagent	Product	Yield (%)	Reference
Methyl cyclohexyl ketone (*Cont'd*)	C$_2$H$_5$ONO, CH$_3$COCl	Methyl α-nitrosocyclohexyl ketone	43	19
Methyl benzyl ketone	NOCl	1-Oximino-1-phenyl-2-propanone	—	182
	C$_5$H$_{11}$ONO, NaOC$_2$H$_5$	1-Oximino-1-phenyl-2-propanone	76	167
4-Phenyl-2-butanone	C$_5$H$_{11}$ONO, NaOC$_2$H$_5$	3-Oximino-4-phenyl-2-butanone	—	205
Benzalacetone	C$_5$H$_{11}$ONO, HCl	1-Oximino-4-phenyl-3-buten-2-one	30–70	34, 205a
Anisacetone	NOCl	1-Oximino-4-*p*-methoxyphenyl-3-buten-2-one	—	182
Methyl *n*-nonyl ketone	C$_5$H$_{11}$ONO, HCl	3-Oximino-2-undecanone	30	206
2,4-Dinitrophenylacetone	C$_5$H$_{11}$ONO, HCl	1-Oximino-1-(2,4-dinitrophenyl)-2-propanone	80	16
	C$_5$H$_{11}$ONO, NaOC$_2$H$_5$	3-Acetyl-6-nitrobenzisoxazole	—	16
Diethyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-3-pentanone	37–55	207
	C$_5$H$_{11}$ONO, HCl	2-Oximino-3-pentanone	30–70	34
Ethyl *n*-propyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-3-hexanone, 4-oximino-3-hexanone	—	17
Ethyl isopropyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-4-methyl-3-pentanone	53	19
		2-Nitroso-2-methyl-3-pentanone	30	20
	C$_2$H$_5$ONO, aq. HCl	2-Nitroso-2-methyl-3-pentanone	20	
		2-Oximino-4-methyl-3-pentanone	7	19
	C$_2$H$_5$ONO, CH$_3$COCl	2-Nitroso-2-methyl-3-pentanone	34	
		2-Oximino-4-methyl-3-pentanone	49	208
Ethyl *n*-butyl ketone	C$_4$H$_{11}$ONO, NaOC$_2$H$_5$	2-Oximino-3-heptanone, 4-oximino-3-heptanone	40	17
Ethyl isobutyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-5-methyl-3-hexanone	—	208
Ethyl *n*-amyl ketone	C$_4$H$_{11}$ONO, NaOC$_2$H$_5$	2-Oximino-3-octanone, 4-oximino-3-octanone	40	17
Ethyl isoamyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-6-methyl-3-heptanone	—	17
Ethyl isohexyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-7-methyl-3-octanone	—	17
Ethyl cyclohexyl ketone	C$_2$H$_5$ONO, HCl	2-Oximino-1-cyclohexyl-1-propanone	39	19
		1-(1-Nitrosocyclohexyl)-1-propanone	4	19
	C$_2$H$_5$ONO, aq. HCl	2-Oximino-1-cyclohexyl-1-propanone	15	19
		1-(1-Nitrosocyclohexyl)-1-propanone	4	19
	C$_2$H$_5$ONO, CH$_3$COCl	2-Oximino-1-cyclohexyl-1-propanone	26	
		1-(1-Nitrosocyclohexyl)-1-propanone	3	18
Ethyl *n*-pentadecyl ketone	C$_5$H$_{11}$ONO, HCl	2-Oximino-3-octadecanone	—	

Note: References 191–316 are listed on pp. 375–377.

* This compound was obtained as an oil of 52% purity. The yield was based upon the weight and analysis of the oil.

† The yield was based on the dioxime isolated.

‡ This yield could not be obtained in a confirmatory study; see ref. 183.

§ The solvent was concentrated hydrochloric acid rather than sulfuric acid.

‖ This was originally believed to be 1-oximino-2-pentanone. Kalischer, *Ber.*, **28**, 1513 (1895)

¶ This compound decomposes slowly when stored in air.

TABLE I—Continued

KETONES

A. Dialkyl Monoketones—Continued

Starting Compound	Method	Products	Yield %	Reference
Ethyl n-heptadecyl ketone	C5H11ONO, HCl	2-Oximino-3-eicosanone	—	18
Di-n-propyl ketone	C5H11ONO, HCl	3-Oximino-4-heptanone	—	209
	NOCl	3-Oximino-4-heptanone	—	193
n-Propyl isopropyl ketone	C5H5ONO, HCl	4-Oximino-2-methyl-3-hexanone	47	19
	C2H5ONO, CH3COCl	4-Oximino-2-methyl-3-hexanone	35	19
Isopropyl n-butyl ketone	C5H5ONO, HCl	4-Oximino-2-methyl-3-heptanone	29	19
	C2H5ONO, CH3COCl	4-Oximino-2-methyl-3-heptanone	46	19
Isopropyl isobutyl ketone	C5H5ONO, HCl	4-Oximino-2,5-dimethyl-3-hexanone	19	19
		2-Nitroso-2,5-dimethyl-3-hexanone	52	
	C2H5ONO, aq. HCl	4-Oximino-2,5-dimethyl-3-hexanone	7	19
		2-Nitroso-2,5-dimethyl-3-hexanone	4	
	C2H5ONO, CH3COCl	4-Oximino-2,5-dimethyl-3-hexanone	8	19
		2-Nitroso-2,5-dimethyl-3-hexanone	50	
Dibenzyl ketone	C2H5ONO, NaOC2H5	1,3-Dioximino-1,3-diphenyl-2-propanone	Small	64
Cyclopentanone	C5H11ONO, CH3COCl	2,5-Dioximinocyclopentanone	—	61
Cyclohexanone	C5H11ONO, HCl	1,2-Cyclohexanedione monoxime nitrite(?)	—	210
	C5H11ONO, CH3COCl	2,6-Dioximinocyclohexanone	—	61
	(+,−)-2-Octyl nitrite, NaOC2H5	1,2-Cyclohexanedione monoxime	69	211
	(+)-2-Octyl nitrite, NaOC2H5	1,2-Cyclohexanedione monoxime	—	211
	2-Ethyl-n-hexyl nitrite, NaOC2H5	1,2-Cyclohexanedione monoxime	80	212
3-Methylcyclohexanone	C5H11ONO, CH3COCl	3-Methyl-2,6-dioximinocyclohexanone	—	63
4-Methylcyclohexanone	(+)-2-Octyl nitrite, NaOC2H5	2-Oximino-1-methylcyclohexanone	—	211
	(−)-2-Octyl nitrite, NaOC2H5	2-Oximino-4-methylcyclohexanone	—	61
6-Oximino-3-methylcyclohexanone	C5H11ONO, CH3COCl	2,6-Dioximino-3-methylcyclohexanone	—	63
2,2,6-Trimethyl-4-piperidone	C5H11ONO, HCl	3,5-Dioximino-2,2,6-trimethyl-4-piperidone	90	62
2,2,6,6-Tetramethyl-4-piperidone	C5H11ONO, CH3COCl	3,5-Dioximino-2,2,6,6-tetramethyl-4-piperidone	50	62
Cycloheptanone	C2H5ONO, NaOC2H5	2,7-Dioximinocycloheptanone	Small	61
Camphor		α-Oximinocamphor	(48)	184
	C5H11ONO, NaOC2H5	α-Oximinocamphor	32, 34	213, 214

Ketone	Reagents	Product	Yield	References
6-Phenylcamphor	$C_5H_{11}ONO$, $NaNH_2$, KNH_2	3-Oximino-6-phenylcamphor	—	215
(−)-Epicamphor	$C_5H_{11}ONO$, $NaNH_2$	(−)-3-Oximinoepicamphor	71 (Cr.)	60
(+)-Carone	$C_5H_{11}ONO$, CH_3COCl	(+)-Nitrosocarone	45	216
Menthone	$C_5H_{11}ONO$, HCl	β,ξ-Dimethyl-ε-oximinocaprylic acid	Poor	59
	$C_5H_{11}ONO$, HCl	4-Nitrosomenthone	8	58
	C_2H_5ONO, CH_3COCl	β,ξ-Dimethyl-ε-oximinocaprylic acid	60	57
	$C_5H_{11}ONO$, $NaOC_2H_5$	4-Nitrosomenthone	40	59
Pulegone	$C_5H_{11}ONO$, HCl	2-Nitrosopulegone	68	217, 218
	$C_5H_{11}ONO$, $NaOC_2H_5$	β,ξ-Dimethyl-ε-oximino-7-octenoic acid	—, 10	59
Dihydrocarvone hydrobromide	C_2H_5ONO, CH_3COCl	1-Nitrosodihydrocarvone hydrobromide	15	57
Dihydroeucarvone	$C_5H_{11}ONO$, HCl	Nitrosodihydroeucarvone	—	216
	HNO_2	Nitrosodihydroeucarvone	—	219
Carvomenthone (tetrahydrocarvone)	C_2H_5ONO, CH_3COCl	1-Nitrosocarvomenthone	—, 18	57, 220
Tropinone	$C_5H_{11}ONO$, HCl	α,α'-Dioximinotropinone	90	65
	$C_5H_{11}ONO$, $NaOC_2H_5$, C_2H_5	α,α'-Dioximinotropinone	—	65
cis-N-Acetyl-7-keto-8-methyldecahydroiso-quinoline	C_2H_5ONO, $NaOC_2H_5$	N-Acetyl-10-oximinodihydrohomomeroquinene ethyl ester	68	6

B. Aryl Alkyl Monoketones

Ketone	Reagents	Product	Yield	References
Acetophenone	CH_3ONO, HCl	α-Oximinoacetophenone	69 **	32
	C_4H_9ONO, HCl	α-Oximinoacetophenone	6–12	31
	C_4H_9ONO, $NaOC_2H_5$	α-Oximinoacetophenone	—, 37	31, 21
	$C_5H_{11}ONO$, $NaOC_2H_5$	α-Oximinoacetophenone	—, 50	28, 30
	$C_5H_{11}ONO$, $NaNH_2$	α-Oximinoacetophenone	32	29
m-Bromoacetophenone	C_4H_9ONO, HCl	α-Oximino-m-bromoacetophenone	75	35
p-Bromoacetophenone	C_4H_9ONO, $NaOC_2H_5$	α-Oximino-p-bromoacetophenone	63	35
m-Chloroacetophenone	C_4H_9ONO, HCl	α-Oximino-m-chloroacetophenone	63	35
p-Chloroacetophenone	C_4H_9ONO, $NaOC_2H_5$	α-Oximino-p-chloroacetophenone	60	35
	$C_4H_{11}ONO$, $NaOC_2H_5$	α-Oximino-p-chloroacetophenone	—	221
	NOCl	α-Oximino-p-chloroacetophenone	—	182
3,4-Dichloroacetophenone	$C_4H_{11}ONO$, Na	α-Oximino-3,4-dichloroacetophenone	5	179
	$C_5H_{11}ONO$, $NaOC_2H_5$	α-Oximino-3,4-dichloroacetophenone	51	179
3-Chloro-4-hydroxyacetophenone	C_4H_9ONO, $NaOC_2H_5$	α-Oximino-3-chloro-4-hydroxyacetophenone	4	21
	C_4H_9ONO, HCl	α-Oximino-3-chloro-4-hydroxyacetophenone	11	21
3-Bromo-4-hydroxyacetophenone	C_4H_9ONO, HCl	α-Oximino-3-bromo-4-hydroxyacetophenone	—	21

Note: References 191–316 are listed on pp. 375–377.
** The yield was calculated on the basis of unrecovered ketone.

TABLE I—*Continued*

KETONES

B. Aryl Alkyl Monoketones—Continued

Starting Compound	Method	Products	Yield %	Reference
p-Methylacetophenone	C₃H₁₁ONO, NaOC₂H₅	α-Oximino-*p*-methylacetophenone	—	222
3,4-Dimethoxyacetophenone	C₃H₁₁ONO, NaOC₂H₅	α-Oximino-3,4-dimethoxyacetophenone	75	23
p-Benzyloxyacetophenone	C₄H₉ONO, NaOC₂H₅	α-Oximino-*p*-benzyloxyacetophenone	77	223
2-Benzyloxy-5-methoxyacetophenone	CH₃ONO, HCl	α-Oximino-2-benzyloxy-5-methoxyacetophenone ††	—	224
2-Benzyloxy-5-ethoxyacetophenone	CH₃ONO, HCl	α-Oximino-2-benzyloxy-5-ethoxyacetophenone ††	—	224
Phenacylpyridinium bromide	C₅H₁₁ONO	α-Oximinophenacylpyridinium bromide	44	225
		α-Oximinophenacylpyridinium bromide	—	225
Phenacyl chloride	HNO₂	Phenylglyoxylohydroxamyl chloride	82, 86	39, 40
p-Methylphenacyl chloride	C₄H₉ONO, HCl	*p*-Tolylglyoxylohydroxamyl chloride	74	39
p-Phenylphenacyl chloride	C₄H₉ONO, HCl	*p*-Xenylglyoxylohydroxamyl chloride	82	39
p-Chlorophenacyl chloride	C₄H₉ONO, HCl	*p*-Chlorophenylglyoxylohydroxamyl chloride	77	39
p-Methoxyphenacyl chloride	C₄H₉ONO, HCl	*p*-Methoxyphenylglyoxylohydroxamyl chloride	82	39
p-Hydroxyphenacyl chloride	C₄H₉ONO, HCl, H₂O	*p*-Hydroxyphenylglyoxylohydroxamyl chloride	95	39
3,4-Dihydroxyphenacyl chloride	C₄H₉ONO, HCl	3,4-Dihydroxyphenylglyoxylohydroxamyl chloride	82	39
Phenyl 2,4-dinitrobenzyl ketone	C₄H₉ONO, HCl	Phenyl α-oximino-2,4-dinitrobenzyl ketone	75	16
α-2-Quinolyl-*o*-carboxyacetophenone	C₅H₁₁ONO, HCl	α-Oximino-α-2-quinolyl-*o*-carboxyacetophenone	—	226
Propiophenone	HNO₂	α-Oximinopropiophenone	65–68, 75	36, 32
	CH₃ONO, HCl	α-Oximinopropiophenone	51, 72	35, 37
	C₄H₉ONO, HCl	α-Oximinopropiophenone	30–70	33, 34
	C₅H₁₁ONO, HCl	α-Oximinopropiophenone	23–24 ‡‡	227
	C₅H₁₁ONO, NaOC₂H₅	α-Oximinopropiophenone	74, 78	37, 180
p-Methylpropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-methylpropiophenone	64, 88	129, 180
p-Phenylpropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-phenylpropiophenone	70	228
p-Nitropropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-nitropropiophenone	75	228
p-Acetamidopropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-acetamidopropiophenone	75	228
p-Benzamidopropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-benzamidopropiophenone	74	228
o-Fluoropropiophenone	C₄H₉ONO, HCl	α-Oximino-*o*-fluoropropiophenone	87	24
m-Fluoropropiophenone	C₄H₉ONO, HCl	α-Oximino-*m*-fluoropropiophenone	88	24
p-Fluoropropiophenone	C₄H₅ONO, HCl	α-Oximino-*p*-fluoropropiophenone	76	24
o-Chloropropiophenone	C₄H₅ONO, HCl	α-Oximino-*o*-chloropropiophenone	83	24
m-Chloropropiophenone	C₄H₉ONO, HCl	α-Oximino-*m*-chloropropiophenone	83, 89	24, 180
p-Chloropropiophenone	C₄H₉ONO, HCl	α-Oximino-*p*-chloropropiophenone		

Substrate	Product (oxime / α-nitroso compound)	Reagent	Yield (%)	References
p-Chloropropiophenone (Cont'd)			Good	
	α-Oximino-p-chloropropiophenone	C_2H_5ONO, HCl	71	35
o-Bromopropiophenone	α-Oximino-o-bromopropiophenone	C_2H_5ONO, HCl	76	24
m-Bromopropiophenone	α-Oximino-m-bromopropiophenone	C_2H_5ONO, HCl	82, 87	24, 35
p-Bromopropiophenone	α-Oximino-p-bromopropiophenone	C_2H_5ONO, HCl	1 §§	35
3-Chloro-4-hydroxypropiophenone	α-Oximino-3-chloro-4-hydroxypropiophenone	C_2H_5ONO, HCl	41	22
o-Methoxypropiophenone	α-Oximino-o-methoxypropiophenone	C_2H_5ONO, HCl	72	22
p-Methoxypropiophenone	α-Oximino-p-methoxypropiophenone	C_2H_5ONO, HCl	90	22
2,4-Dimethoxypropiophenone	α-Oximino-2,4-dimethoxypropiophenone	C_2H_5ONO, HCl	50-75	224
2,5-Diethoxypropiophenone	α-Oximino-2,5-diethoxypropiophenone	CH_3ONO, HCl	50-75	224
2,5-Dibenzyloxypropiophenone	α-Oximino-2,5-dibenzyloxypropiophenone	CH_3ONO, HCl	50-75	224
2-Benzyloxy-5-methoxypropiophenone	α-Oximino-2-benzyloxy-5-methoxypropiophenone	CH_3ONO, HCl	—	229
o-Carbomethoxypropiophenone	α-Oximino-o-carbomethoxypropiophenone	CH_3ONO, HCl	—	224
2-Ethylcarbonato-5-methoxypropiophenone	α-Oximino-2-ethylcarbonato-5-methoxypropiophenone	C_2H_5ONO, HCl	38	22
m-Hydroxypropiophenone	α-Oximino-m-hydroxypropiophenone	CH_3ONO, HCl	60 ‖	22
p-Hydroxypropiophenone	α-Oximino-p-hydroxypropiophenone	C_4H_9ONO, HCl	56	22
3-Hydroxy-4-methylpropiophenone	α-Oximino-3-hydroxy-4-methylpropiophenone	C_4H_9ONO, HCl	72 ‖	22
3-Methyl-4-hydroxypropiophenone	α-Oximino-3-methyl-4-hydroxypropiophenone	C_4H_9ONO, HCl	27	22
3,4-Dihydroxypropiophenone	α-Oximino-3,4-dihydroxypropiophenone	C_4H_9ONO, HCl	—	230
	Acetophenone oxime		—	231
β-Phenylpropiophenone	α-Oximino-β-phenylpropiophenone	$C_5H_{11}ONO$, $NaOC_2H_5$	50	31
Butyrophenone	α-Oximinobutyrophenone	$C_5H_{11}ONO$, $NaOC_2H_5$	50	31
p-Methylbutyrophenone	α-Oximino-p-methylbutyrophenone	C_2H_5ONO, HCl	81	229
o-Carbomethoxybutyrophenone	α-Oximino-o-carbomethoxybutyrophenone	C_2H_5ONO, HCl	69	31
Valerophenone	α-Oximinovalerophenone	C_2H_5ONO, HCl	55-60	31
Caprophenone	α-Oximinocaprophenone	C_2H_5ONO, HCl	25	31
Caprylophenone	α-Oximinocaprylophenone	C_2H_5ONO, HCl	—	232
δ-o-Aminobenzoylvaleric acid	4-Hydroxy-3-cinnolinebutyric acid	HNO_2	45	233, 234, 235
1-Acetonaphthone	α-Oximino-1-acetonaphthone	$C_5H_{11}ONO$, $NaOC_2H_5$	—	234
4-Methoxy-1-acetonaphthone	α-Oximino-4-methoxy-1-acetonaphthone	$C_5H_{11}ONO$, $NaOC_2H_5$	74	180
1-Propionaphthone	α-Oximino-1-propionaphthone	C_4H_9ONO, HCl	68	180
2-Propionaphthone	α-Oximino-2-propionaphthone	C_4H_9ONO, HCl	—	236
Desoxybenzoin (sodium salt)	Benzil monoxime	N_2O_3 ¶¶		

Note. References 191-316 are listed on pp. 375-377.

†† The oxime was reduced, without isolation, to the debenzylated amino ketone.

‡‡ The yield was based on the dioximo isolated.

§§ The yield was based on the amino ketone isolated.

‖ The yield was calculated on the basis of unrecovered ketone.

¶¶ Prepared from sodium nitrite and sulfuric acid.

TABLE I—Continued

KETONES

B. Aryl Alkyl Monoketones—Continued

Starting Compound	Method	Products	Yield %	Reference
Deoxybenzoin (Cont'd)	C₅H₁₁ONO, NaOC₂H₅	Benzil monoxime	61	236
	C₂H₅ONO, Na	2-Furoic acid	—	237
Deoxyfuroin	C₂H₅ONO, Na	2-Furaldehyde oxime	—	237
		2-Furoic acid	—	
Deoxybenzfuroin	C₂H₅ONO, Na	Benzaldehyde oxime	—	40a
1-Indanone	HNO₂	2-Oximino-1-indanone	56	42
	C₅H₁₁ONO, HCl	2-Oximino-1-indanone	Nearly quant.	41
3-Methyl-1-indanone	C₅H₁₁ONO, HCl	2-Oximino-3-methyl-1-indanone	Nearly quant.	43
5,6-Methylenedioxy-1-indanone	C₅H₁₁ONO, HCl	2-Oximino-5,6-methylenedioxy-1-indanone	Nearly quant.	43
5,6-Dimethoxy-1-indanone	C₅H₁₁ONO, HCl	2-Oximino-5,6-dimethoxy-1-indanone	Nearly quant.	238
Narcein	C₅H₁₁ONO, NaOC₂H₅	α-Oximinonarcein	80	239
Nornarcein	C₂H₅ONO, NaOC₂H₅	α-Oximinonornarcein	—	239
Methylhydrastein	C₂H₅ONO, NaOC₂H₅	α-Oximinomethylhydrastein	—	240
Methyl 4-quinolyl ketone	C₅H₁₁ONO, NaOC₂H₅	Oximinomethyl-4-quinolyl ketone	60	38
Ethyl 4-quinolyl ketone	C₂H₅ONO, NaOC₂H₅	2-Oximino-1-(4-quinolyl)-1-propanone	—	241
o-Nitrophenylpyruvic acid	NaNO₂, CH₃CO₂H	o-O₂NC₆H₄CCOCO₂H * (as bisphenylhydrazone)	—	
		o-Nitrobenzonitrile	—	

C. β-Diketones

Reactant	Reagent	Product	Yield	Reference
Acetylacetone	HNO$_2$	3-Oximino-2,4-pentanedione	—, 78	52, 51
	C$_5$H$_{11}$ONO	3-Oximino-2,4-pentanedione	44	46
2,4-Hexanedione	HNO$_2$	3-Oximino-2,4-hexanedione	86	242
3,5-Heptanedione	C$_5$H$_{11}$ONO, HCl	4-Oximino-3,5-heptanedione	43	46
1-Phenyl-1,3-butanedione	N$_2$O$_3$, ether	2-Nitroso-1-phenyl-1,3-butanedione	—	50
	N$_2$O$_3$, C$_2$H$_5$OH, NaOC$_2$H$_5$	2-Oximino-1-phenyl-1,3-butanedione	97	44
	HNO$_2$	2-Oximino-1-phenyl-1,3-butanedione	—	51
1-o-Methoxyphenyl-1,3-butanedione	HNO$_2$	2-Oximino-1-o-methoxyphenyl-1,3-butanedione	—	49
1-o,p-Dimethoxyphenyl-1,3-butanedione	HNO$_2$	2-Oximino-1-o,p-dimethoxyphenyl-1,3-butanedione	50–60	49
Dibenzoylmethane	N$_2$O$_3$, ether	2-Nitroso-1,3-diphenyl-1,3-propanedione	80	50
	C$_5$H$_{11}$ONO, HCl	2-Nitroso-1,3-diphenyl-1,3-propanedione	35	48
1-Phenyl-3-p-methoxyphenyl-1,3-propane-dione	N$_2$O$_3$, ether	2-Nitroso-1-phenyl-3-p-methoxyphenyl-1,3-propanedione		50
	C$_5$H$_{11}$ONO, HCl	2-Oximino-1-phenyl-3-p-methoxyphenyl-1,3-propanedione	—	50
1-Phenyl-3-p-nitrophenyl-1,3-propanedione	C$_5$H$_{11}$ONO, HCl	2-Oximino-1-phenyl-3-p-nitrophenyl-1,3-propanedione †	—	50
1,4-Diphenyl-1,3-butanedione	C$_5$H$_{11}$ONO, HCl	2-Oximino-1,4-diphenyl-1,3-butanedione	—, 99	243
5,5-Dimethyl-1,3-cyclohexanedione (methone)	HNO$_2$	2-Oximino-5,5-dimethyl-1,3-cyclohexanedione		47, 45
	CH$_3$ONO, NaOC$_2$H$_5$	2-Oximino-5,5-dimethyl-1,3-cyclohexanedione	—	46
5-Phenyl-1,3-cyclohexanedione	HNO$_2$	2-Oximino-5-phenyl-1,3-cyclohexanedione	—	47
1,3-Indanedione	HNO$_2$	2-Nitroso-1,3-indanedione	—, Quant, (crude)	54, 53
1-(3'-Methoxy-4'-hydroxyphenyl)-2,6-dicarbethoxycyclohexane-3,5-dione	HNO$_2$	1-(3'-Methoxy-4'-hydroxyphenyl)-2,6-dicarbethoxy-4-oximinocyclohexane-3,5-dione		244
1-(3'-Methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxycyclohexane-3,5-dione	HNO$_2$	1-(3'-Methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxy-4-oximinocyclohexane-3,5-dione	85	244
3,5,8,10-Tetraketo-3,4,5,8,9,10-hexahydropyrene	HNO$_2$	4,9-Dinitroso-3,5,8,10-tetraketo-3,4,5,8,9,10-hexahydropyrene	89	56

D. Imine Derivatives (Amino-Ketones)

Reactant	Reagent	Product	Yield	Reference
2-Methyl-3,3-dimethylpseudoindole	HNO$_2$	2-Oximinomethyl-3,3-dimethylpseudoindole	—	66
2-Methyl-3,3-diethylpseudoindole	HNO$_2$	2-Oximinomethyl-3,3-diethylpseudoindole	—	245
1,3,3-Trimethyl-2-methyleneindoline	HNO$_2$, HClO$_4$	1,3,3-Trimethyl-2-formoximeindolenium 1-perchlorate	96	67

Note: References 191–316 are listed on pp. 375–377.

* These products were obtained when the reaction was run in hot acetic acid. No reaction took place at room temperature. When an aqueous solution of o-nitrophenylpyruvic acid was boiled with sodium nitrite (2 equiv.) and hydrochloric acid (2 equiv.), o-nitrosobenzoile was produced in 85% yield.

† A quantitative yield of the corresponding triketone was obtained when a benzene solution of the diketone was treated with nitrous fumes.

TABLE II

β-Keto Acids, Esters, and Related Compounds

Starting Compound	Method	Products	Yield %	Reference
		A. β-Keto Acids		
Ethyl acetoacetate	HOH; HNO₂	Oximinoacetone	75–80	246
	HOH; HNO₂	Oximinoacetone	—, 12	247, 68
	HOH; HNO₂	Oximinoacetone	60, 70 *	248, 249
	HOH; HNO₂	1-Oximino-3-ethoxy-2-propanone	—	250
	HOH; HNO₂			251
Ethyl γ-ethoxyacetoacetate	HNO₂	Diacetyl monoxime	—, 60 *	70, 252
Barium α-methylacetoacetate	HOH; HNO₂	Diacetyl monoxime	71,† 98	5, 202
Ethyl α-methylacetoacetate		Diacetyl monoxime	, 94	5, 71, 202
		3-Oximino-2-pentanone	40	189
Ethyl α-ethylacetoacetate	HOH; HNO₂	3-Oximino-5-ethoxy-2-pentanone	—, 50 ‡	202, 253, 264
Ethyl α-2-ethoxyethylacetoacetate	HOH; HNO₂	3-Oximino-2-hexanone		202, 255
Ethyl α-propylacetoacetate	HOH; HNO₂	3-Oximino-4-methyl-2-pentanone	—, 80	254, 256
Ethyl α-isopropylacetoacetate	HOH; HNO₂	3-Oximino-5-hexen-2-one		257
Ethyl α-allylacetoacetate	HOH; HNO₂	3-Oximino-5-methyl-2-hexanone	—, 75	258, 70
Ethyl α-isobutylacetoacetate	HOH; HNO₂	3-Oximino-2-octanone	—, 60	259, 33
Ethyl α-amylacetoacetate	HOH; HNO₂	3-Oximino-6-methyl-2-heptanone	80	70
Ethyl α-isoamylacetoacetate	HOH; HNO₂	3-Oximino-4-methyl-2-decanone	80	70
α-sec-Octylacetoacetic acid	NOCl	3-Oximino-4-methyl-2-butanone	—	251
α-Benzylacetoacetic acid	HNO₂	3-Oximino-4-phenyl-2-butanone	80–90	260
Ethyl α-benzylacetoacetate	HOH; HNO₂	3-Oximino-4-phenyl-2-butanone	—	260a
Ethyl α-m-xylylacetoacetate	HOH; HNO₂	3-Oximino-4-m-tolyl-2-butanone	—	70
Ethyl α-ethyl-β-ketocaproate	HOH; NOCl	3-Oximino-4-heptanone	—	70
Ethyl α-propyl-β-ketoenanthate	HOH; NOCl	5-Oximino-4-octanone	—	70
Ethyl α-isopropyl-β-ketocaproate	HOH; NOCl	3-Oximino-2-methyl-4-heptanone	80	70
Ethyl 2-ethyl-3-keto-5-methylhexanoate	HOH; NOCl	3-Oximino-6-methyl-4-heptanone	80	70
α-Methyl-β-ketocaprylic acid	NOCl	2-Oximino-3-octanone	85	70
α-Ethyl-β-ketocaprylic acid	NOCl	3-Oximino-4-nonanone		70
Ethyl α-methylbenzoylacetate	HOH; HNO₂	α-Oximinopropiophenone	—	261, 262
Ethyl α-ethylbenzoylacetate	HOH; HNO₂	α-Oximinobutyrophenone	—	263
Diethyl acetylsuccinate	HOH; HNO₂	β-Oximino-γ-ketovaleric acid	—	262
Diethyl α-acetylglutarate	HOH; HNO₃	γ-Oximino-δ-ketohexanoic acid	50, 51	264
Acetonedicarboxylic acid	HNO₂	Dioximinoacetone	—, 20	75, 72
	HNO₂	Dioximinoacetone		73, 74, 249
Diethyl α,α′-diacetylsuccinate	HOH; HNO₂	3,4-Dioximino-2,5-hexanedione	20–30	263

Compound	Product	Reagent	Yield (%)	References
Diethyl α,α'-diacetylsuccinate (Cont'd)	3,6-Diimino-2,5-hexanedione	HOH; HNO₂	Very small	343
Diethyl α-acetyl-α-methylsuccinate	3-Acetyl-4-methyl-5-isoxazolone(?)	HOH; HNO₂	—	343
2-Carboxycyclohexanone	1,2-Cyclohexanedione monoxime	HNO₂	—	371
2-Carbethoxycyclohexanone	2,5-Dioximinocyclohexanone	HOH; HNO₂	49.4	74,75
	1,2-Cyclohexanedione monoxime	HOH; HNO₂	7.2	74,75
	1,2-Cyclohexanedione monoxime	HOH; HNO₂	—	74
2-Carbethoxy-5-methylcyclohexanone	2-Oximino-5-methylcyclohexanone	HOH; HNO₂	54	74,64
2-Carbethoxy-6-methylcyclohexanone	2-Oximino-6-methylcyclohexanone	HOH; HNO₂	—	74
Menthonecarboxylic acid	4-Oximinomenthone	HNO₂	—	343

B. β-Keto Esters and Amides

Compound	Product	Reagent	Yield (%)	References
Methyl acetoacetate	Methyl oximinoacetate	NO₂SO₃H	—	345
Ethyl acetoacetate	Ethyl oximinoacetate	NO₃SO₃H	7.5	242,245
	Ethyl α-oximinoacetoacetate	HNO₂	—	4,64,242
	Ethyl α-oximinoacetoacetate	HNO₂	75–79	5,61,191, 192,220, 272,300
Ethyl α-oximinoacetoacetate		HNO₂	98–99	272,300
Ethyl α-oximinoacetoacetate		CH₃ONO, HCl	94	94
Ethyl α-oximinoacetoacetate		CH₃ONO, NaOC₂H₅	—	93
Ethyl α-oximinoacetoacetate		C₄H₉ONO	—	4,5,220
Isobutyl acetoacetate	Isobutyl α-oximinoacetate	NO₃SO₃H	70	245
Ethyl β-ketovalerate	Ethyl α-oximino-β-ketovalerate	HNO₂	—	92
Methyl benzoylacetate	Methyl α-oximinobenzoylacetate	HNO₂	—	272
Ethyl benzoylacetate	Ethyl α-oximinobenzoylacetate	HNO₃	7.91	55,276, 277,278
Ethyl benzoylacetate	Ethyl α-oximinobenzoylacetate	C₅H₁₁ONO	—	349
Methyl o-methoxybenzoylacetate	Methyl α-oximino-o-methoxybenzoylacetate	HNO₂	—	379
Methyl m-methoxybenzoylacetate	Methyl α-oximino-m-methoxybenzoylacetate	HNO₂	—	379
Methyl p-methoxybenzoylacetate	Methyl α-oximino-p-methoxybenzoylacetate	HNO₂	—	379
Ethyl m-methoxybenzoylacetate	Ethyl α-oximino-m-methoxybenzoylacetate	HNO₂	—	379
Ethyl p-methoxybenzoylacetate	Ethyl α-oximino-p-methoxybenzoylacetate	HNO₂	—	379
Ethyl p-nitrobenzoylacetate	Ethyl α-oximino-p-nitrobenzoylacetate	N₂O₃, ether	—	281

Note: References 191–316 are listed on pp. 375–377.
* The yield was based on the dioxime isolated.
† The yield was calculated on the basis of unrecovered ester.
‡ The yield was based on the diketone isolated.

TABLE II—Continued

β-Keto Acids, Esters, and Related Compounds

Starting Compound	Method	Products	Yield %	Reference
		B. β-Keto Esters and Amides—Continued		
Diethyl acetonedicarboxylate	C₂H₅ONO (1 eq.), HCl	Diethyl α-oximino-β-ketoglutarate	Almost quant.	96
	C₂H₅ONO (1 eq.), HCl	Diethyl α-oximino-β-ketoglutarate	—	97
	C₂H₅ONO (3 eq.), HCl	3,5-Dicarbethoxy-4-hydroxyisoxazole	66	97
Ethyl furoylacetate	HNO₂	Ethyl α-oximinofuroylacetate	65	282
Ethyl picolinoylacetate	HNO₂	Ethyl α-oximinopicolinoylacetate	—	171
Ethyl nicotinoylacetate	HNO₂	Ethyl α-oximinonicotinoylacetate	—	172
Tetronic acid	HNO₂	α-Oximinotetronic acid	—	283
γ-Phenyltetronic acid	HNO₂	α-Oximino-γ-phenyltetronic acid	—	284
Bentotetronic acid	HNO₂	α-Oximinobenzotetronic acid	—	285
Acetoacetanilide	HNO₂	α-Oximinoacetoacetnilide	—	286
	HNO₂	α-Oximinoacetoacetanilide	—	287
Acetoacet-o-toluidide	NOCl	α-Oximinoacetoacet-o-toluidide	—	287
Acetoacet-p-toluidide	NOCl	α-Oximinoacetoacet-p-toluidide	—	287
Acetoacet-2,1-dimethylanilide	NOCl	α-Oximinoacetoacet-2,4-dimethylanilide	—	287
N-α-Naphthylacetoacetamide	NOCl	α-Oximino-N-α-naphthylacetoacetamide	—	287
N-β-Naphthylacetoacetamide	NOCl	α-Oximino-N-β-naphthylacetoacetamide	—	287
Ethyl α-formylpropionate	N₂O₃	Ethyl α-nitrosoisopropionate	95	82
Ethyl α-formylphenylacetate	N₂O₃	Ethyl oximino-?-nitrophenylacetate	<1	82
Methyl α-methylacetoacetate	NO₂SO₃H	Methyl α-oximinopropionate	65	288
	NOCl	Methyl α-oximinopropionate	—	10
Ethyl α-methylacetoacetate	NO₂SO₃H	Ethyl α-oximinopropionate	—	268
	N₂O₃	Ethyl α-nitrosopropionate	Quant.	85
	HNO₂	Ethyl α-oximinopropionate	18	68
	HNO₂; HOH	α-Oximinopropionic acid	—	68, 289
	C₂H₅ONO, 85% H₂SO₄	Ethyl α-oximinopropionate	88	92
Ethyl α-ethylacetoacetate	NO₂SO₃H	Ethyl α-oximinobutyrate	—, 90	268, 288, 290
	N₂O₃	Ethyl α-nitrosobutyrate	Quant.	85
	HNO; HOH	α-Oximinobutyric acid	—	291
	C₂H₅ONO, 85% H₂SO₄; HOH	α-Oximinobutyric acid	80	92
Ethyl α-n-propylacetoacetate	NO₂SO₃H	Ethyl α-oximinovalerate	—, 83	268, 288
	HNO; HOH	α-Oximinovaleric acid	—	292

Starting material	Reagents	Product	Yield (%)	References
Ethyl α-n-propylacetoacetate (Cont'd)	C₂H₅ONO, 85% H₂SO₄; HOH	α-Oximinovaleric acid	85	92
Isobutyl α-n-propylacetoacetate	NO₂SO₃H	Isobutyl α-oximinovalerate	—, 75	200, 288
Ethyl α-isopropylacetoacetate	NO₂SO₃H	Ethyl α-oximinoisovalerate	93	288
	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximinoisovalerate	74	164
Ethyl α-n-butylacetoacetate	N₂O₃	Ethyl α-nitrosocaproate	Quant.	85
	NO₂SO₃H	Ethyl α-oximinocaproate	—	290
	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximinocaproate	84	162
	C₄H₉ONO, 85% H₂SO₄; HOH	α-Oximinocaproic acid	86, 89	9, 92
Ethyl α-isobutylacetoacetate	NO₂SO₃H	Ethyl α-oximinoisocaproate	—, 90	290, 288
Ethyl α-sec-butylacetoacetate	C₂H₅ONO, 85% H₂SO₄; HOH	α-Oximino-β-methylvaleric acid	70	91
	NO₂SO₃H	Ethyl α-oximino-β-methylvalerate	75	83
Ethyl α-isoamylacetoacetate	N₂O₃	Ethyl 2-nitroso-5-methylhexanoate	Quant	288
	NO₂SO₃H	Ethyl 2-oximino-5-methylhexanoate	90	259
	C₂H₅ONO, NaOC₂H₅	Ethyl 2-oximino-5-methylhexanoate	—	288
Ethyl α-sec-octylacetoacetate	NO₂SO₃H	Ethyl α-oximino-β-methylpelargonate	80	102
Ethyl α-2-bromoethylacetoacetate	NO₂SO₃H	Ethyl α-oximino-γ-bromobutyrate	Low	155
Ethyl α-3-diethylaminopropylacetoacetate	N₂O₃, NaOC₂H₅	Ethyl α-oximino-δ-diethylaminovalerate	26	293
Ethyl α-methyl-β-ketovalerate	NO₂SO₃H	Ethyl α-oximinopropionate	—	88
Ethyl α-ethyl-β-ketocaprylate	C₄H₉ONO, 85% H₂SO₄	Ethyl α-oximinobutyrate	85	92
Diethyl acetylsuccinate	N₂O₃	Diethyl oximinosuccinate	—	84, 85
	NO₂SO₃H	Diethyl nitrososuccinate	60	118
Diethyl α-acetylglutarate	C₂H₅ONO, KOC₂H₅	Diethyl α-oximinoglutarate	80	118
	C₄H₉ONO, 85% H₂SO₄	Diethyl α-oximinoglutarate	91	92
	N₂O₃	Diethyl α-oximinoglutarate	—	85
Diethyl α,α'-diacetylsuccinate	N₂O₃	Diethyl α-nitroso-α'-acetylsuccinate	70–80	294
Ethyl α-benzylacetoacetate	C₄H₉ONO, 85% H₂SO₄; HOH	Ethyl α-oximino-β-phenylpropionate	85, 89	9, 92
	C₄H₉ONO, 85% H₂SO₄; H₃PO₄ (1:2); HOH	α-Oximino-β-phenylpropionic acid	45	9
	C₄H₉ONO, (CH₃CO)₂O; HOH	α-Oximino-β-phenylpropionic acid	Small	9
	C₄H₉ONO, HCO₂H; HOH	α-Oximino-β-phenylpropionic acid	Small	9
	C₅H₉ONO, HCl; HOH	α-Oximino-β-phenylpropionic acid	52	9
	C₄H₉ONO, NaOC₂H₅; HOH	α-Oximino-β-phenylpropionic acid	62	9
	HNO₂; HOH	α-Oximino-β-phenylpropionic acid	Small	9
Ethyl m-xylylacetoacetate	C₂H₅ONO, 85% H₂SO₄; HOH	α-Oximino-β-m-tolylpropionic acid	87	260a
Ethyl α-p-methoxybenzylacetoacetate	C₂H₅ONO, 85% H₂SO₄; HOH	α-Oximino-β-p-methoxyphenylpropionic acid	62	92
Ethyl 3,4-methylenedioxybenzylacetoacetate	i-C₃H₇ONO, NaOC₂H₅; HOH	α-Oximino-β-3,4-methylenedioxyphenylpropionic acid		101

Note: References 101–316 are listed on pp. 375–377.

TABLE II—Continued

β-Keto Acids, Esters, and Related Compounds

Starting Compound	Method	Products	Yield %	Reference
B. β-Keto Esters and Amides—Continued				
Methyl α-methylbenzoylacetate	NO_2SO_3H	Methyl α-oximinopropionate	—	10
	RONO ($NaOC_2H_5$)	Methyl α-oximinopropionate	—	10
Ethyl α-methylbenzoylacetate	N_2O_3	Ethyl α-nitroso-α-methylbenzoylacetate	Quant.	295
Diethyl benzoylsuccinate	N_2O_3	Diethyl oximinosuccinate	60	82
2-Carbethoxycyclopentanone	C_2H_5ONO, $NaOC_2H_5$	Diethyl α-oximinoadipate	60–80	87
	C_2H_5ONO, CH_3COCl	2-Nitroso-2-carbethoxycyclopentanone	—	87
2-Carbethoxycyclohexanone	C_2H_5ONO, $NaOC_2H_5$	Diethyl α-oximinopimelate	30	87
	C_2H_5ONO, CH_3COCl	2-Nitroso-2-carbethoxycyclohexanone	25–30	86
2-Carbethoxy-4-methylcyclopentanone	N_2O_4, $NaOC_2H_5$	Diethyl α-oximino-γ-methyladipate	50	86
	C_2H_5ONO, $NaOC_2H_5$	Diethyl α-oximino-γ-methyladipate	30	86
	C_2H_5ONO, CH_3COCl	2-Nitroso-2-carbethoxy-4-methylcyclopentanone	25–51	296
2,5-Dicarbethoxy-1,4-cyclohexanedione	N_2O_3, ether	2,5-Dinitroso-2,5-dicarbethoxy-1,4-cyclohexanedione	70	297
α-Acetyl-γ-butyrolactone	HNO_2	α-Oximino-γ-butyrolactone	85–91	95
	C_2H_5ONO, HCl	α-Oximino-γ-butyrolactone	81	94
α-Acetyl-δ-chloro-γ-valerolactone	HNO_2	α-Oximino-δ-chloro-γ-valerolactone	67	93
	NO_2SO_3H	α-Oximino-δ-chloro-γ-valerolactone	90	99
	$NaNO_2$	α-Oximinopropionylglycolic acid	57	99
α-Methyltetronic acid	N_2O_3, CH_3CO_2H	α-Nitroso-α-methyltetronic acid	65	100
α-Ethyltetronic acid	$NaNO_2$	α-Oximinotetronic acid	—	100
α-Benzyltetronic acid	$NaNO_2$	α-Oximino-β-phenylpropionylglycolic acid	73	46
Ethyl N-methyl-N-phenylcarbamylpyruvate	$C_6H_{11}ONO$, $NaOC_2H_5$	Ethyl oximino-(N-methyl-N-phenylcarbamyl)pyruvate	—	—
C. β-Imino Acids and Esters and β-Keto Imino Ethers				
Ethyl β-aminocrotonate	HNO_2	Ethyl α-oximino-β-iminobutyrate	—	81
	$C_5H_{11}ONO$	Ethyl α-oximino-β-nitrosiminobutyrate (ammonium salt)	—	80
Monoethyl α-cyano-β-iminoglutaric acid	HNO_2	Ethyl α-cyano-β-imino-γ-oximinobutyrate	—	79
β-Phenyliminobutyric acid	HNO_2	α-Phenyliminopropionaldehyde oxime	—	81
Benzoylacetimido ethyl ether	$C_5H_{11}ONO$, NH_3	Oximinobenzoylacetamidine	—	26
	$C_5H_{11}ONO$, HCl	Oximinobenzoylacetimido ethyl ether	—	26
		Ethyl α-oximinobenzoylacetate	—	26
Benzoylacetimido ethyl ether hydrochloride	$NaNO_2$	Oximinobenzoylacetimido ethyl ether	—	26

Note: References 191–316 are listed on pp. 375–377.

TABLE III

MALONIC ACIDS, ESTERS, AND AMIDES

Starting Compound	Method	Products	Yield %	Reference
Methylmalonic acid	C₂H₅ONO, HCl	α-Oximinopropionic acid	90	9
Ethylmalonic acid	C₂H₅ONO, HCl	α-Oximinobutyric acid	89	9
β-Bromoethylmalonic acid	NaNO₂,*	α-Oximino-γ-butyrolactone	70-80	102
n-Butylmalonic acid	C₄H₉ONO, HCl	α-Oximinocaproic acid	87	9
Isobutylmalonic acid	C₂H₅ONO, HCl †	α-Oximinoisocaproic acid	75-85	12
Benzylmalonic acid	NaNO₂,*	α-Oximino-β-phenylpropionic acid	62	102
	HNO₂	α-Oximino-β-phenylpropionic acid	40-48	12
	C₂H₅ONO, HCl	α-Oximino-β-phenylpropionic acid	90	12
	C₄H₉ONO, HCl	α-Oximino-β-phenylpropionic acid	90	9
γ-Methoxybenzylmalonic acid	i-C₃H₇ONO, HCl	α-Oximino-β-p-methoxyphenylpropionic acid	92	9
3,4-Methylenedioxybenzylmalonic acid	HNO₂	α-Oximino-β-3,4-methylenedioxyphenylpropionic acid	85-90	101
α-Carboxy-γ-butyrolactone	HOH, HNO₂	α-Oximino-γ-butyrolactone	34	297
Diethyl phthalimidoacetylmalonate	CH₃ONO, NaOCH₃	1-Oximino-3-phthalimidoacetyl-2-propanone	—	298
Dimethyl malonate	HNO₂	Dimethyl oximinomalonate	60, 70, —	103
Diethyl malonate	HNO₂	Diethyl oximinomalonate	80-90 ‡	*104, 107, 108, 113*
	N₂O₃, NaOC₂H₅	Diethyl oximinomalonate	50 (max.)	104
	N₂O₃, NaOC₂H₅	Diethyl oximinomalonate	Consider-able amt.	105
				106
Diethyl methylmalonate	N₂O₃, NaOC₂H₅	Diethyl oximinomalonate	90-95	111
	CH₃ONO, NaOC₂H₅	Diethyl oximinomalonate	85-90	103, 110
	C₂H₅ONO, NaOC₂H₅	Diethyl oximinomalonate	87	112
	N₂O₃, NaOC₂H₅	Ethyl α-oximinopropionate	Consider-able amt.	299
Diethyl ethylmalonate	C₂H₅ONO, NaOC₂H₅; HOH	α-Oximinobutyric acid	65	9
Diethyl n-butylmalonate	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximinocaproate	80	8
	C₂H₅ONO, NaOC₂H₅; HOH	α-Oximinocaproic acid	70	9
Diethyl benzylmalonate	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximino-β-phenylpropionate	92	8
	C₂H₅ONO, NaOC₂H₅; HOH	α-Oximino-β-phenylpropionic acid	75	9
α-Carbethoxy-γ-butyrolactone	HNO₂	α-Nitroso-α-carbethoxy-γ-butyrolactone	50-56	297
	N₂O₃	α-Nitroso-α-carbethoxy-γ-butyrolactone	—	297

Note: References 191-310 are listed on pp. 375-377.

* The reaction vessel was sealed tightly before it was shaken with each portion of the reagent.

† No reaction took place with sodium nitrite and sulfuric acid.

‡ Three moles of nitrous acid were used in this experiment. One mole and two moles gave only 50 and 63% yields, respectively, of oxime.

TABLE III—*Continued*

MALONIC ACIDS, ESTERS, AND AMIDES

Starting Compound	Method	Products	Yield %	Reference
Diethyl γ-cyanopropylmalonate	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximino-δ-cyanovalerate	90, 93	158, 114
	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximino-δ-cyanovalerate	70–83	157
	C₂H₅ONO, NaOC₂H₅	Ethyl α-oximino-δ-diethylaminovalerate	94	8
Diethyl γ-diethylaminopropylmalonate	C₂H₅ONO, NaOC₂H₅	Diethyl 1-(o-nitrophenyl)-3-oximinoglutarate	62	300
Diethyl 1-(o-nitrophenyl)propane-1,3,3-tricarboxylate				
Diethyl acetylmalonate	HNO₂	Ethyl α-oximinoacetoacetate	—	301
Malonamide	HNO₂	Oximinomalonamide	70	115
	N₂O₃, H₂O	Oximinomalonamide	40	116
	NOCl, CH₃CO·C₂H₅, C₂H₅OH §	Oximinomalonamide	Quant.	117
N,N'-Dimethylmalonamide	NOCl	α-oximino-N,N'-dimethylmalonamide	Quant.	117
N,N'-Diphenylmalonamide	NOCl	α-oximino-N,N'-diphenylmalonamide	Quant.	117
N,N'-Di-o-tolylmalonamide	NOCl	α-oximino-N,N'-di-o-tolylmalonamide	Quant.	117
N-p-Tolylmalonamide	NOCl	α-oximino-N-p-tolylmalonamide	—	117
N,N'-Di-p-tolylmalonamide	NOCl	α-oximino-N,N'-di-p-tolylmalonamide	Quant.	117
Ethyl N-p-tolylmalonamide	NOCl	Ethyl α-oximino-N-p-tolylmalonamate	Quant.	117
N,N'-Di-α-naphthylmalonamide	NOCl	α-oximino-N,N'-α-naphthylmalonamide	Quant.	117
N,N'-Di-β-naphthylmalonamide	NOCl	α-oximino-N,N'-di-β-naphthylmalonamide	Poor	117
N,N'-Dimethyl-N,N'-diphenylmalonamide	NOCl	α-oximino-N,N'-dimethyl-N,N'-diphenylmalonamide	—	117
Malonyldiurethane	HNO₂	Oximinomalonyldiurethane	—	115

Note: References 191–316 are listed on pp. 375–377.

§ The solvent is noted because poor yields were obtained with chloroform as solvent and when the nitrosation was run with liquid nitrosyl chloride in a sealed tube (see ref. 110).

TABLE IV

ARYLACETIC ACIDS AND ESTERS

Starting Compound	Method	Products	Yield %	Reference
Ethyl phenylacetate	C₂H₅ONO, KOC₂H₅	Ethyl α-oximinophenylacetate	70	118
Ethyl p-bromophenylacetate	C₂H₅ONO, KOC₂H₅	Ethyl α-oximino-p-bromophenylacetate	Good	118
Ethyl o-nitrophenylacetate	C₅H₁₁ONO, NaOC₂H₅	Ethyl α-oximino-o-nitrophenylacetate	—	119
Ethyl p-nitrophenylacetate	C₅H₁₁ONO, NaOC₂H₅	Ethyl α-oximino-p-nitrophenylacetate	—	119
Methyl 2,4-dinitrophenylacetate	C₅H₁₁ONO, NaOCH₃	3-Carbomethoxy-δ-nitrobenzisoxazole	85	16
2-Nitro-4-aminophenylacetic acid	C₅H₁₁ONO, HCl	3-Nitro-4-oximinomethylphenyldiazonium chloride	—	120
Ethyl 2-nitro-4-aminophenylacetate	C₅H₁₁ONO, HCl	Ethyl α-oximino-o-nitrophenylacetate	—	120

Note: References 191–316 are listed on pp. 375–377.

TABLE V

NITRILES

Starting Compound	Method	Products	Yield %	Reference
Methyl cyanoacetate	HNO_2	Methyl oximinocyanoacetate	90–95	123
	HNO_2	Methyl oximinocyanoacetate	—	122
	$C_5H_{11}ONO, NaOCH_3$	Methyl oximinocyanoacetate	Poor	123
Ethyl cyanoacetate	HNO_2	Ethyl oximinocyanoacetate	87–100	122, 123, 125
	HNO_2	Ethyl oximinocyanoacetate	—	124, 302
	$C_5H_{11}ONO, NaOC_2H_5$	Ethyl oximinocyanoacetate	Poor	123
Cyanoacetamide	HNO_2	Oximinocyanoacetamide	70	122
Cyanoacetylurea	$NaNO_2$	Oximinocyanoacetylurea	—, 89	129, 122
N-Methyl-N'-cyanoacetylurea	HNO_2	N-Methyl-N'-oximinocyanoacetylurea	—	129
Ethyl cyanoacetylcarbamate	HNO_2	Ethyl oximinocyanoacetylcarbamate	—	122
Ethyl α-cyanobutyrate	$RONO, KOC_2H_5$	α-Oximinobutyronitrile	—	126
Ethyl cyanophenylacetate	$RONO, KOC_2H_5$	Oximinophenylacetonitrile	Small	126
Ethyl α-cyano-β-phenylpropionate	$C_5H_{11}ONO, KOC_2H_5$	α-Oximino-β-phenylpropionitrile	—	126
Phenylacetonitrile	N_2O_3	Oximinophenylacetonitrile	—	303
	$RONO, NaOC_2H_5$	Oximinophenylacetonitrile	50	128
p-Bromophenylacetonitrile	$C_5H_{11}ONO, NaOC_2H_5$	Oximino-p-bromophenylacetonitrile	—	127
o-Chlorophenylacetonitrile	$C_5H_{11}ONO, NaOC_2H_5$	Oximino-o-chlorophenylacetonitrile	—	127
p-Chlorophenylacetonitrile	$C_5H_{11}ONO, NaOC_2H_5$	Oximino-p-chlorophenylacetonitrile	55	128
p-Nitrophenylacetonitrile	$C_5H_{11}ONO, NaOC_2H_5$	Oximino-p-nitrophenylacetonitrile	61	128
β-Imino-β-phenylpropionitrile	HNO_2, HCl	α-Oximino-β-nitrosimino-β-phenylpropionitrile	63	128
	$C_5H_{11}ONO$	α-Oximino-β-nitrosimino-β-phenylpropionitrile	—	133
		Oximinobenzoylacetonitrile	—	132
β-Imino-β-p-tolylpropionitrile	$C_5H_{11}ONO$	α-Oximino-β-nitrosimino-β-p-tolylpropionitrile (ammonium salt)	—	132
β-Iminobutyronitrile	$C_5H_{11}ONO$	Oximino-p-toluylacetonitrile	Very small amount	132
		α-Oximino-β-nitrosiminobutyronitrile (ammonium salt)		
Succinonitrile	$C_5H_{11}ONO, KOC_2H_5$	Dioximinosuccinonitrile	Small	118
Malononitrile	HNO_2	Oximinomalononitrile	—	131
	$C_5H_{11}ONO, NaOC_2H_5$	α-Oximino-β-amino-β-ethoxy-β-hydroxypropionitrile	88–92	130
Cyanodihydrocarvone	$C_5H_{11}ONO, NaOC_2H_5$	$CH_3C\!=\!CH\!-\!CH_2\!-\!C\!-\!C\overset{CH_3}{\underset{N}{\|}}$ $\|\quad\quad\quad\quad CH_2\ CH_2CONHC\!-\!O$	66	304, 305
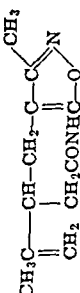
Note: References 191–316 are listed on pp. 375–377.

TABLE VI

Nitro Compounds

Method	Products	Yield %	Reference
HSO₄	Methyl nitrolic acid	—, 27 (max.)	1, 306, 307, 308
HSO₃	Ethyl nitrolic acid	—, 65	1, 306
HSO₃	Ethyl nitrolic acid	49	309, 310
HNO₃	Ethyl nitrolic acid	82, 90	136, 311
HNO₃	Propyl nitrolic acid	—	306
HNO₃	Propyl nitrolic acid	60	134, 310
N₂O₃, H₂O	Propyl pseudonitrole	53	134
HSO₃	Propyl pseudonitrole	70	2, 310
HSO₃	Butyl nitrolic acid	—	312
HSO₃	Isobutyl nitrolic acid	—, 78	313, 3
HSO₃	Isobutyl pseudonitrole	—	186
HNO₃	Cyclohexyl pseudonitrole	—	314
HNO₃	Camphene pseudonitrole	—	315
HNO₃	Hydroxyethyl nitrolic acid	33	137
HNO₃	Methyl nitrolic acid	—	316
HNO₃	Ethyl nitrolic acid	—	137
HNO₂	Hydroxyethyl nitrolic acid	—	137
HNO₂	o-Nitrobenzaldehyde oxime	—	139, 141
C₅H₁₁ONO, NaOC₂H₅	p-Nitrobenzaldehyde oxime	—	138, 139, 141
C₅H₁₁ONO, NaOC₂H₅	2-Nitro-4-methylbenzaldehyde oxime	—	139
C₅H₁₁ONO, NaOC₂H₅	4-Nitrosalicylonitrile	1	16
C₅H₁₁ONO, NaOC₂H₅	o-Nitroacetophenone oxime	—	140
C₅H₁₁ONO, NaOC₂H₅	o-Nitrobenzophenone oxime	—	140
C₅H₁₁ONO, NaOC₂H₅	3,4'-Dinitrobenzophenone oxime	—	140
C₅H₁₁ONO, NaOC₂H₅	Phenyl-p-nitrobenzohydroximic acid	—	140

Starting compounds (left column):
1-Nitrobutane
2-Nitrobutane
1-Nitro-2-methylpropane
Nitrocyclohexane
α-Nitrocamphene
β-Nitroethanol
2-Nitro-1-propanol
2-Nitro-1,3-propanediol
o-Nitrotoluene
p-Nitrotoluene
Nitro-p-xylene
2,4-Dinitrotoluene
o-Nitroethylbenzene
o-Nitrodiphenylmethane
3,4'-Dinitrodiphenylmethane
Phenyl p-nitrobenzyl ether

Note: References 191-316 are listed on pp. 375-377.

TABLE VII

Hydrocarbons

Starting Compound	Method	Products	Yield %	Reference
n-Heptane	NOCl, sunlight	Di-n-propyl ketone oxime	—	145
Toluene	NOCl, sunlight	Benzaldehyde oxime	Pract. quant.	146
Cyclopentadiene	C₅H₁₁ONO, NaOC₂H₅	Oximinocyclopentadiene	70-90	143

Note: References 191-316 are listed on pp. 375-377.

REFERENCES TO TABLES I–VI

[191] Behrend and Tryller, *Ann.*, **283**, 209 (1894).
[192] Sandmeyer, *Ber.*, **20**, 639 (1887).
[193] Lynn and Lee, *J. Am. Pharm. Assoc.*, **16**, 309 (1927).
[194] Kalischer, *Ber.*, **28**, 1513 (1895).
[195] Adams and Kamm, *J. Am. Chem. Soc.*, **40**, 1281 (1918).
[196] Biltz, *Z. anal. Chem.*, **48**, 164 (1909).
[197] Gandarin, *J. prakt. Chem.*, [2] **77**, 414 (1908).
[198] Diels and Farkas, *Ber.*, **43**, 1958 (1910).
[199] Diels and Jost, *Ber.*, **35**, 3292 (1902).
[200] Ajello and Sigillò, *Gazz. chim. ital.*, **69**, 57 (1939).
[201] Ponzio, *Ann. chim. applicata*, **13**, 342 (1923) [*Chem. Zentr.*, **1924**, I, 2396].
[202] Ponzio, *Gazz. chim. ital.*, **51**, 213 (1921).
[203] Knorr and Hess, *Ber.*, **44**, 2758 (1911).
[204] Holleman, *Rec. trav. chim.*, **10**, 214 (1895).
[205] Ponzio, *Gazz. chim. ital.*, **35**, 394 (1905).
[205a] Foulds and Robinson, *J. Chem. Soc.*, **103**, 1768 (1913).
[206] Fileti and Ponzio, *J. prakt. Chem.*, [2] **50**, 374 (1894).
[207] Jänecke, *Ber.*, **32**, 1095 (1899).
[208] Ponzio, *Gazz. chim. ital.*, **27**, 271 (1897).
[209] Ponzio and Borelli, *Gazz. chim. ital.*, **32**, 423(1902).
[210] Wilson and Read, *J. Chem. Soc.*, **1935**, 1273
[211] Pezold and Shriner, *J. Am. Chem. Soc.*, **54**, 4707 (1932).
[212] Rauh, Smith, Banks, and Diehl, *J. Org. Chem.*, **10**, 199 (1945).
[213] Claisen and Manasse, *Ber.*, **22**, 530 (1889).
[214] Claisen and Manasse, *Ann.*, **274**, 73 (1893).
[215] Bredt, Heinemann, and Goblet, *J. prakt. Chem.*, [2] **98**, 104 (1918).
[216] Baeyer, *Ber.*, **28**, 639 (1895).
[217] Baeyer and Henrich, *Ber.*, **28**, 654 (1895).
[218] Baeyer and Prentice, *Ber.*, **29**, 1078 (1896).
[219] Baeyer, *Ber.*, **27**, 1923 (1894).
[220] Baeyer and Oehler, *Ber.*, **29**, 33 (1896).
[221] Avogadro, *Gazz. chim. ital.*, **53**, 698 (1923).
[222] Müller and Pechmann, *Ber.*, **22**, 2560 (1889).
[223] Priestley and Moness, *J. Org. Chem.*, **5**, 359 (1940).
[224] Ide and Baltzly, *J. Am. Chem. Soc.*, **70**, 1084 (1948).
[225] Kröhnke and Kübler, *Ber.*, **70**, 1117 (1937).
[226] Eibner and Hofmann, *Ber.*, **37**, 3013 (1904).
[227] Avogadro, *Gazz. chim. ital.*, **54**, 545 (1924).
[228] Hartung and Foster, *J. Am. Pharm. Assoc.*, **35**, 15 (1946).
[229] Ullyot, Taylor, and Dawson, *J. Am. Chem. Soc.*, **70**, 542 (1948).
[230] Ney, *Ber.*, **21**, 2448 (1882).
[231] Schneidewind, *Ber.*, **21**, 1326 (1888).
[232] Witkop, *J. Am. Chem. Soc.*, **72**, 1428 (1950).
[233] Lister and Robinson, *J. Chem. Soc.*, **101**, 1307 (1912).
[234] Madinaveitia, *Bull. soc. chim. France*, [4] **25**, 605 (1919).
[235] Pictet and Manevitch, *Arch. sci. phys. nat.*, **35**, 40 (1913) [*C. A.*, **7**, 1713 (1913)].
[236] Meyer and Oelkers, *Ber.*, **21**, 1295 (1888).
[237] Kariyone, *J. Pharm. Soc. Japan*, **1917**, No. 428, 899 [*C. A.*, **12**, 275 (1918)].
[238] Freund and Oppenheim, *Ber.*, **42**, 1097 (1909).
[239] Rabe and McMillian, *Ann.*, **377**, 223 (1910).
[240] Kaufmann, Kunkler, and Peyer, *Ber.*, **46**, 62 (1913).
[241] Reissert, *Ber.*, **30**, 1030 (1897).
[242] Küster, *Chem. Zelle u. Gewebe*, **12**, 15 (1924–1926) (*Chem. Zentr.*, **1925**, I, 2079).

[243] Bülow and Grotowsky, *Ber.*, **34**, 1487 (1901).
[244] Papadakis, Scigliano, Chin, and Adrian, *J. Am. Chem. Soc.*, **72**, 4256 (1950).
[245] Plancher, *Ber.*, **31**, 1494 (1898).
[246] Charrier, *Gazz. chim. ital.*, **37**, 145 (1907).
[247] Ceresole, *Ber.*, **15**, 1326 (1882).
[248] Tschugaev, *J. Russ. Phys. Chem. Soc.*, **42**, 1466 (1910) [*C. A.*, **6**, 594 (1912)].
[249] Dey, *J. Chem. Soc.*, **105**, 1039 (1914).
[250] Weizmann, Stephen, and Agashe, *J. Chem. Soc.*, **103**, 1857 (1913).
[251] Ceresole, *Ber.*, **15**, 1871 (1882).
[252] Tschugaeff, *Ber.*, **38**, 2522, footnote (1905).
[253] Treadwell, *Ber.*, **14**, 2159 (1881).
[254] Otte and Pechmann, *Ber.*, **22**, 2115 (1889).
[255] Westenberger, *Ber.*, **16**, 2991 (1883).
[256] Sarasin, *Helv. Chim. Acta*, **6**, 380 (1923).
[257] Treadwell and Westenberger, *Ber.*, **15**, 2788 (1882).
[258] Ponzio and Prandi, *J. prakt. Chem.*, [2] **58**, 401 (1898); *Gazz. chim. ital.*, **28**, 280 (1898).
[259] Bouveault and Locquin, *Compt. rend.*, **135**, 295 (1902).
[260] Sonn, *Ber.*, **40**, 4666 (1907).
[260a] Ryan, *Ber.*, **31**, 2130 (1898).
[261] Pechmann and Müller, *Ber.*, **21**, 2119 (1888).
[262] Müller and Pechmann, *Ber.*, **22**, 2127 (1889).
[263] Thal, *Ber.*, **25**, 1718 (1892).
[264] Baldracco, *J. prakt. Chem.*, [2] **49**, 197 (1894).
[265] Treibs and Dinelli, *Ann.*, **517**, 152 (1935).
[266] Oddo, *Gazz. chim. ital.*, **27**, 108 (1897).
[267] Bouveault and Wahl, *Bull. soc. chim. France*, [3] **31**, 675 (1904).
[268] Inglis and Knight, *J. Chem. Soc.*, **93**, 1595 (1908).
[269] Bouveault and Wahl, *Ber.*, **38**, 927 (1905).
[270] Wleügel, *Ber.*, **15**, 1050 (1882).
[271] Jovitschitsch, *Ber.*, **28**, 2683 (1895).
[272] Nussberger, *Ber.*, **25**, 2152 (1892).
[273] Bouveault and Wahl, *Bull. soc. chim. France*, [3] **33**, 559 (1905).
[274] Wahl, *Bull. soc. chim. France*, [4] **3**, 949 (1908).
[275] Perkin, *J. Chem. Soc.*, **47**, 244 (1885).
[276] Baeyer and Perkin, *Ber.*, **16**, 2133 (1883).
[277] Wahl, *Bull. soc. chim. France*, [4] **1**, 465 (1907).
[278] Wolff and Hall, *Ber.*, **36**, 3614 (1903).
[279] Wahl and Silberzweig, *Bull. soc. chim. France*, [4] **11**, 61 (1912).
[280] Wahl and Silberzweig, *Bull. soc. chim. France*, [4] **11**, 25 (1912).
[281] Perkin and Bellenot, *J. Chem. Soc.*, **49**, 449 (1886).
[282] Torrey and Zanetti, *Am. Chem. J.*, **44**, 410 (1910).
[283] Wolff, *Ann.*, **291**, 244 (1896).
[284] Anschütz and Böcker, *Ann.*, **368**, 67 (1910).
[285] Anschütz, *Ann.*, **367**, 210 (1909).
[286] Knorr, *Ann.*, **236**, 80 (1886).
[287] Naik, Trivedi, and Mankad, *J. Indian Chem. Soc.*, **20**, 384 (1943).
[288] Locquin, *Bull. soc. chim. France*, [3] **31**, 1068 (1904).
[289] Gutknecht, *Ber.*, **13**, 1116 (1880).
[290] Godfrin, *J. pharm. chim.*, **30**, 323 (1939).
[291] Wleügel, *Ber.*, **15**, 1057 (1882).
[292] Fürth, *Ber.*, **16**, 2180 (1883).
[293] Hantzsch and Wohlbrück, *Ber.*, **20**, 1322 (1887).
[294] Hall, Hynes, and Lapworth, *J. Chem. Soc.*, **107**, 135 (1915).
[295] Schmidt and Aeckerle, *Ann.*, **398**, 251 (1913).
[296] Ebert, *Ann.*, **229**, 55 (1885).

[297] Feofilaktov and Onishchenko, *J. Gen. Chem. (U.S.S.R.)*, **9**, 304 (1939) [*C. A.*, **34**, 378 (1940)].

[298] Bradshaw, Stephen, and Weizmann, *J. Chem. Soc.*, **107**, 808 (1915).

[299] Bergreen, *Ber.*, **20**, 533 (1887).

[300] Kotake, Sakan, and Miwa, *J. Am. Chem. Soc.*, **72**, 5085 (1951).

[301] Lang, *Ber.*, **20**, 1327 (1887).

[302] DePaolini and Imberti, *Gazz. chim. ital.*, **58**, 198, footnote (1928).

[303] Meyer, A., *Ber.*, **21**, 1314 (1888).

[304] Lapworth and Wechsler, *J. Chem. Soc.*, **91**, 977 (1907).

[305] Lapworth and Wechsler, *J. Chem. Soc.*, **91**, 1919 (1907).

[306] Meyer and Constam, *Ann.*, **214**, 328 (1882).

[307] Tscherniak, *Ber.*, **8**, 114 (1875).

[308] Tscherniak, *Ann.*, **180**, 166 (1876).

[309] Meyer, *Ber.*, **7**, 425 (1874).

[310] Meyer, *Ann.*, **175**, 88 (1875).

[311] Graul and Hantzsch, *Ber.*, **31**, 2863 (1898).

[312] Demole, *Ber.*, **7**, 790 (1874).

[313] Meyer and Locher, *Ann.*, **180**, 135 (1876).

[314] Nametkin, *J. Russ. Phys. Chem. Ges.*, **42**, 585 (1910) (*Chem. Zentr.*, **1910**, II, 1377).

[315] Nametkin and Zabrodin, *Ann.*, **441**, 186 (1923).

[316] Demuth and Meyer, *Ann.*, **256**, 42 (1890).

CHAPTER 7

EPOXIDATION AND HYDROXYLATION OF ETHYLENIC COMPOUNDS WITH ORGANIC PERACIDS

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CONTENTS

INTRODUCTION

Oxiranes (α-epoxy compounds) and α-glycols can be prepared from olefins by a variety of methods. One of the most important and most generally applicable of these is the oxidation of ethylenic compounds with organic peracids, as exemplified by the accompanying equations.

$$-\overset{|}{C}=\overset{|}{C}- + RCO_3H \rightarrow -\overset{|}{C}\underset{O}{\diagdown\diagup}\overset{|}{C} + RCO_2H \rightarrow$$

$$-\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{OCOR}{C}}- \xrightarrow{\text{Hydrolysis}} -\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{OH}{C}}- + RCO_2H$$
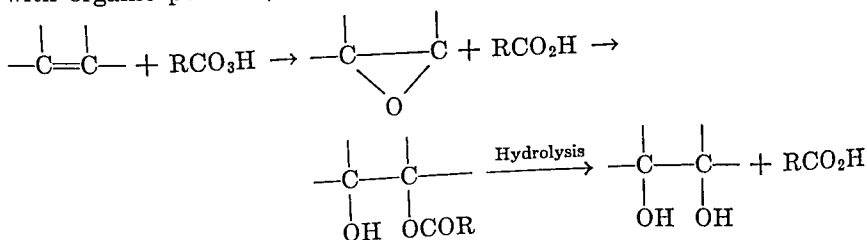
Depending upon the peracid employed and/or the operating conditions, either an oxirane [1,2,3] or an α-glycol [2,4] can be obtained in good yield. Ordinarily the oxirane isolated can be hydrolyzed to the α-glycol.[5] It is important to note that the oxidation step both in epoxidation and hydroxylation reactions with organic peracids is the conversion of the olefin to the oxirane.

The literature on the epoxidation and hydroxylation of compounds containing an isolated ethylenic linkage is so extensive that no attempt has been made to include conjugated systems in a comprehensive fashion. However, occasional comments on α,β-unsaturated acids are found on pp. 385 and 388, the preferential epoxidation of one ethylenic linkage in isoprene is described on p. 397, and a limited number of conjugated dienes and α,β-unsaturated acids are included in Table I.

[1] Findley, Swern, and Scanlan, J. Am. Chem. Soc., 67, 412 (1945).
[2] Swern, Billen, and Scanlan, J. Am. Chem. Soc., 68, 1504 (1946).
[3] Swern, Findley, and Scanlan, J. Am. Chem. Soc., 66, 1925 (1944).
[4] Swern, Billen, Findley, and Scanlan, J. Am. Chem. Soc., 67, 1786 (1945).
[5] Swern, J. Am. Chem. Soc., 70, 1235 (1948).

SCOPE

Epoxidation

Perbenzoic Acid. The discovery that oxiranes can be prepared from ethylenic compounds by epoxidation with an organic peracid is generally credited to the Russian chemist, Prileschajew,[6-9] who showed that perbenzoic acid is an efficient oxidizing agent for the epoxidation of isolated double bonds. This reaction is excellent for preparative pur-

$$-\overset{|}{C}=\overset{|}{C}- + C_6H_5CO_3H \xrightarrow[\text{solvents}]{\text{Organic}} -\overset{|}{C}\overset{}{\underset{\diagdown \diagup}{\underset{O}{\quad}}}\overset{|}{C}- + C_6H_5CO_2H$$
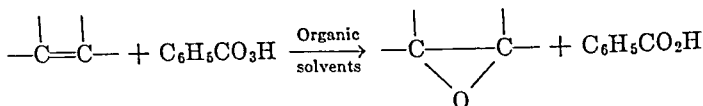
poses. It proceeds under mild conditions, and it is generally conducted in a non-reactive organic solvent, such as chloroform, ether, benzene, acetone or dioxane. The reaction time is usually short, but it varies with the number and nature of the groups attached to the ethylenic system.[10] As a rule the yields are high.

Most investigators have preferred to prepare a solution of perbenzoic acid [3,11-15] for epoxidation. However, since perbenzoic acid can be prepared conveniently by the oxidation of benzaldehyde with oxygen,[3,16-19] some investigators have treated solutions of benzaldehyde and the unsaturated compound with air or oxygen, the perbenzoic acid being consumed as it is formed. This application of the perbenzoic acid epoxidation technique, in which separate preparation and isolation of the peracid is avoided, has been applied to the oxidation of methyl oleate,[20] oleyl alcohol,[20] octenes,[21] oleic acid,[3,22] stilbene,[22] styrene,[22] and squalene,[22] and good yields of oxiranes were generally obtained. When

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[6] Prileschajew, *Ber.*, **42**, 4811 (1909).

[7] Prileschajew, *J. Russ. Phys. Chem. Soc.*, **42**, 1387 (1910) [*J. Chem. Soc. Abstr.*, **100**, I, 255 (1910)].

[8] Prileschajew, *J. Russ. Phys. Chem. Soc.*, **43**, 609 (1911) [*C. A.*, **6**, 348 (1912)].

[9] Prileschajew, *J. Russ. Phys. Chem. Soc.*, **44**, 613 (1912) [*C. A.*, **6**, 2407 (1912)].

[10] Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).

[11] Braun, *Org. Syntheses, Coll. Vol.* **1**, 431, 2nd ed. (1941).

[12] Hibbert and Burt, *J. Am. Chem. Soc.*, **47**, 2240 (1925).

[13] Kolthoff, Lee, and Mairs, *J. Polymer Sci.*, **2**, 199 (1947).

[14] Levy and Lagrave, *Bull. soc. chim. France*, [4] **37**, 1597 (1925).

[15] Tiffeneau, *Org. Syntheses*, **8**, 30 (1928).

[16] Jorissen and van der Beek, *Rec. trav. chim.*, **45**, 245 (1926).

[17] Jorissen and van der Beek, *Rec. trav. chim.*, **46**, 42 (1927).

[18] Jorissen and van der Beek, *Rec. trav. chim.*, **49**, 138 (1930).

[19] van der Beek, *Rec. trav. chim.*, **47**, 286 (1928).

[20] Swern and Findley, *J. Am. Chem. Soc.*, **72**, 4315 (1950).

[21] Pigulevskii, *J. Gen. Chem. (U.S.S.R.)*, **4**, 616 (1934) [*C. A.*, **29**, 2145 (1935)].

[22] Raymond, *J. chim. phys.*, **28**, 480 (1931).

aliphatic aldehydes, such as acetaldehyde and butyraldehyde, are employed instead of benzaldehyde, poor yields of oxiranes result.[20,21,23]

Epoxidation with perbenzoic acid has been employed in the preparation of oxiranes from an extremely large number and wide variety of ethylenic compounds (see Table I).

Monoperphthalic Acid. Another reagent that has been employed in the preparation of oxiranes is monoperphthalic acid; but this reagent, although efficient, has not been studied so extensively as perbenzoic acid, primarily because it offers only minor advantages in most reactions. When the epoxidation requires a long period of time for completion, however, the greater stability of monoperphthalic acid,[24,25] compared to perbenzoic acid, is an advantage. Furthermore, since epoxidations with monoperphthalic acid are usually conducted in chloroform solution and the phthalic acid formed is insoluble, it is readily separated from the oxidation product. Although Böhme [26,27] was apparently the first to demonstrate that monoperphthalic acid is consumed by reaction with the ethylenic linkage, Chakravorty and Levin [25] were the first to isolate oxiranes by the oxidation of unsaturated compounds with this oxidizing agent. Epoxidation with monoperphthalic acid is conducted under the same conditions as with perbenzoic acid, and good yields of oxiranes are obtained. Epoxidation with monoperphthalic acid has been applied most extensively to naturally occurring products, such as sterols and polyenes. Ethylenic compounds which have been converted to oxiranes by epoxidation with monoperphthalic acid are listed in Table I.

Peracetic Acid. Since peracetic acid is one of the most conveniently prepared organic peracids, a study of its possible use as an epoxidizing agent was to be expected. For a long time, however, it was assumed that oxiranes could not be prepared by the epoxidation of olefins with peracetic acid since the products isolated from such reactions were either α-glycols or their monoacetates. The first successful epoxidation with peracetic acid was reported by Böeseken, Smit, and Gaster,[28,29] who obtained methyl 9,10,12,13-diepoxystearate from methyl linoleate, but the yields were extremely poor and the major proportion of the product consisted of a polymer of undetermined constitution.[30] In a systematic study of the reaction of unsaturated compounds with peracetic acid in

[23] Findley and Swern, U. S. pat. 2,567,930 [C. A., **46**, 3560 (1952)].
[24] Baeyer and Villiger, Ber., **34**, 762 (1901).
[25] Chakravorty and Levin, J. Am. Chem. Soc., **64**, 2317 (1942).
[26] Böhme, Ber., **70**, 379 (1937).
[27] Böhme and Steinke, Ber., **70**, 1709 (1937).
[28] Böeseken, Smit, and Gaster, Proc. Acad. Sci. Amsterdam, **32**, 377 (1929).
[29] Smit, Rec. trav. chim., **49**, 675 (1930).
[30] Swern, unpublished results.

acetic acid solution and in inert solvents, Arbusow and Michailow [31,32] observed that hydroxy acetates were formed in acetic acid while good yields of oxiranes were obtained in inert solvents. They concluded that the behavior of peracetic acid toward olefins is the same as that of perbenzoic acid, but that when an acetic acid solution is employed the oxirane is converted to the hydroxy acetate by further reaction with acetic acid. The apparent necessity for employing peracetic acid in an inert solvent to obtain good yields of oxiranes discouraged the general use of peracetic acid for epoxidation, because peracetic acid can be prepared and used most conveniently in acetic acid, whereas its isolation free (or substantially free) of acetic acid is time-consuming and hazardous.

Subsequently, however, in connection with a kinetic study of the reaction of peracetic acid in acetic acid solution with various long-chain olefins, suitable reaction conditions were determined for the efficient conversion of ethylenic compounds to oxiranes.[1] To obtain good yields of oxiranes it is necessary to operate at moderate temperatures (20–25° is preferred), to keep the reaction time as short as possible and to exclude strong acids, which catalyze the opening of the oxirane ring by acetic acid. The reaction was shown to be general and afforded a simple and convenient method for the preparation of oxirane compounds in quantity. Isolation of pure peracetic acid and employment of inert solvents were unnecessary. Yields of oxiranes, however, were usually lower than when perbenzoic or monoperphthalic acid was employed. In the peracetic acid epoxidation of compounds containing both an ethylenic and an acetylenic linkage, it has been reported that only the double bond is attacked.[33,34] Acetylenic compounds react with peracetic acid, but the rates of reaction are only about one-thousandth as great as the rates of reaction of analogous ethylenic compounds. Three atoms of oxygen add, and the acetylenic linkage is cleaved. Oxirenes, $-C{=\!=\!=}C-$, are

$$\begin{array}{c} -C{=\!=\!=}C- \\ \diagdown \diagup \\ O \end{array}$$

intermediates and have been isolated from some reactions.[34a]

Ethylenic compounds which have been converted to oxiranes by epoxidation with peracetic acid are listed in Table I.

Percamphoric Acid. Percamphoric acid has been employed to convert pinene and cholesterol to the corresponding oxiranes.[35]

[31] Arbusow and Michailow, *J. prakt. Chem.*, **127**, 1 (1930).

[32] Arbusow and Michailow, *J. prakt. Chem.*, **127**, 92 (1930).

[33] Malenok and Sologub, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 150 (1940) [*C. A.*, **34**, 7286 (1940)].

[34] Malenok and Sologub, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 983 (1941) [*C. A.*, **37**, 355 (1943)].

[34a] Schlubach and Franzen, *Ann.*, **577**, 60 (1952).

[35] Milas and Cliff, *J. Am. Chem. Soc.*, **55**, 352 (1933).

Performic Acid. Performic acid is generally considered not to be an epoxidation reagent because the high acidity of formic acid (employed either as solvent or formed in the oxidation) causes most oxirane rings to open rapidly. It has been shown recently, however, that α-diisobutylene yields an isolable oxirane on oxidation with performic acid, although the yield is low.[36] By employing only small quantities of formic acid as solvent and oxygen carrier, and in some cases by adding small amounts of sodium hydroxide, it has been reported that methyl oleate, octyl oleate, propylene glycol dioleate, and soybean oil can be converted to oxiranes in fair yields.[37] Recently, two steroids have been converted to oxiranes by epoxidation with performic acid.[38,39]

The diisobutylenes behave somewhat abnormally on reaction with both performic and peracetic acids, yielding, besides the expected products, unsaturated alcohols, an aldehyde, a ketone, a cyclic diether, and high-boiling products.[36,40-43]

Hydroxylation

Peracetic Acid. The use of peracetic acid for the preparation of α-glycols from unsaturated substances probably exceeds that of all other organic peracids combined. Peracetic acid is usually prepared and employed in either of two ways: (1) the peracid is preformed by the reaction of acetic acid or acetic anhydride with 25–90% hydrogen peroxide[1,44-47] and then mixed with the unsaturated compound, or (2) the unsaturated compound is mixed with hydrogen peroxide and acetic acid, and the peracetic acid is consumed as it is formed.[4,48] Under suitable conditions (p. 381) oxiranes are obtained in good yields; but in the manner that the reactions have usually been carried out (long reaction times, and/or high temperatures, and/or in the presence of sulfuric acid), the products isolated are hydroxy acetates formed by the reaction of excess acetic acid with the oxirane produced initially. The hydroxy

[36] Byers and Hickinbottom, *J. Chem. Soc.*, **1948**, 1328.
[37] Niederhauser and Koroly, U. S. pat. 2,485,160 [*C. A.*, **44**, 7346 (1950)].
[38] Djerassi, Mancera, Stork, and Rosenkranz, *J. Am. Chem. Soc.*, **73**, 4496 (1951).
[39] Stork, Romo, Rosenkranz, and Djerassi, *J. Am. Chem. Soc.*, **73**, 3546 (1951).
[40] Byers and Hickinbottom, *J. Chem. Soc.*, **1948**, 284.
[41] Byers and Hickinbottom, *Nature*, **158**, 341 (1946).
[42] Hickinbottom, *J. Chem. Soc.*, **1948**, 1331.
[43] Hickinbottom, *Nature*, **159**, 844 (1947).
[44] D'Ans and Frey, *Ber.*, **45**, 1845 (1912).
[45] D'Ans and Frey, *Z. anorg. Chem.*, **84**, 145 (1914).
[46] D'Ans and Kneip, *Ber.*, **48**, 1136 (1915).
[47] Greenspan, *J. Am. Chem. Soc.*, **68**, 907 (1946).
[48] Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).

acetates are readily hydrolyzable to α-glycols in excellent yield.[49–52] Although good yields of glycols were reported by some early investigators, the operating conditions employed caused the loss of much active oxygen by decomposition. With sulfuric acid as the catalyst, moderate temperatures (40°), and short reaction periods, excellent yields of α-glycols are obtained with stoichiometric quantities of 25–30% hydrogen peroxide.[4] Since the sulfuric acid catalyzes the formation of peracetic acid and the peracid is rapidly consumed at 40°, the reaction is complete in a few hours and little active oxygen is lost. This procedure is one of the most efficient for converting long-chain olefins to α-glycols. Slightly higher yields of α-glycols are obtained when 90% hydrogen peroxide is employed.[48]

Ethylenic compounds which have been converted to α-glycols by oxidation with peracetic acid, either preformed or prepared and utilized *in situ*, are listed in Table I. Some of the unsaturated substances listed have been converted to hydroxy acetates rather than to α-glycols, but the conversion to glycols is effected so readily by hydrolysis that these substances have also been included.

Performic Acid. An even more efficient and rapid hydroxylation technique consists in the reaction of unsaturated compounds with performic acid.[4] Not only is performic acid formed rapidly when 25–90% hydrogen peroxide and formic acid are mixed,[44–47, 53] but it also reacts rapidly and completely with the unsaturated linkage. By means of this hydroxylation reaction, conversion of an unsaturated compound to an α-glycol is accomplished within a short time, and approximately stoichiometric quantities of hydrogen peroxide can be employed. The initial product of oxidation is not the α-glycol but the oxirane, which is rapidly converted in most cases to a hydroxy formate as a result of the high acidity of formic acid. Hydroxy formates are the products usually isolated and are readily converted to the α-glycols by hydrolysis with dilute aqueous alkali or even by exposure to moist air or heating with water.[5] It is important to note that performic acid is preferably not prepared separately, because it is unstable and loses oxygen rapidly,[46,47, 53, 54] but it is prepared and utilized *in situ*.[4] Somewhat more complete hydroxylation is obtained by employing 90% hydrogen peroxide instead of the 25–30% concentration.[48]

Concentrated solutions of performic acid can be used in the hydroxyl-

[49] Hibbitch. *J. Chem. Soc.*, **1926, 1828**.
[51] Hibbitch and Lea, *J. Chem. Soc.*, **1927, 3106**.
[53] Scanlan and Swern. *J. Am. Chem. Soc.*, **62**, 2305 (1940).
[52] Scanlan and Swern, *J. Am. Chem. Soc.*, **62**, 2309 (1940).
[53] Townsley and Homiller, *J. Am. Chem. Soc.*, **64**, 3054 (1942).
[54] Swern and Findley, unpublished results.

ation of α,β-unsaturated acids to give fair yields of dihydroxy acids within a relatively short time.[55] Dilute solutions of organic peracids either are ineffective in hydroxylation of such compounds, or extremely long reaction times are required during which loss of active oxygen occurs.

The performic acid oxidation of ethylenic compounds having a hydroxyl group on a carbon atom directly adjacent to the ethylenic group yields appreciable amounts of acidic chain cleavage products in addition to about 50% of the expected hydroxylation products.[56]

In the peracetic and performic acid hydroxylation of compounds containing both an ethylenic and an acetylenic linkage only the double bond is attacked.[34a, 57-60]

Ethylenic compounds converted to α-glycols by oxidation with performic acid are listed in Table I.

Perbenzoic, Monoperphthalic, or Percamphoric Acid. These acids can be employed for the preparation of α-glycols from olefins by hydrolyzing the oxiranes which are formed first. In general, there is no advantage in employing the aromatic peracids to prepare α-glycols when two more-efficient peracids (performic and peracetic acid) are available for this purpose. In the presence of water or with unusually long reaction times, reactions have been reported in which α-glycols or their monobenzoates rather than oxiranes were obtained from oxidations of olefins with perbenzoic acid.

Ethylenic compounds which have been converted to α-glycols or to hydroxybenzoates by oxidation with perbenzoic acid are listed in Table I.

STEREOCHEMISTRY AND MECHANISM

Although the structure of organic peracids, usually written RCO_3H, is not known, it is evident from their numerous and varied reactions that they are electrophilic reagents.[10] As the nucleophilic nature of an olefin is increased by replacement of the hydrogen atoms of its ethylenic linkage with electron-releasing groups, the rate of reaction with organic peracids increases considerably (see p. 388). Since peracid reactions investigated so far are subject to general acid catalysis,[61, 62] it has been

[55] English and Gregory, *J. Am. Chem. Soc.*, **69**, 2120 (1947).
[56] Ross, Gebhart, and Gerecht, *J. Am. Chem. Soc.*, **71**, 282 (1949).
[57] Evans, Fraser, and Owen, *J. Chem. Soc.*, **1949**, 248.
[58] Malenok, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 1947 (1939) [*C. A.*, **34**, 4385 (1940)].
[59] Malenok and Sologub, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 1904 (1936) [*C. A.*, **31**, 4285 (1937)].
[60] Raphael, *J. Chem. Soc.*, **1949**, S44.
[61] Friess, *J. Am. Chem. Soc.*, **71**, 2571 (1949).
[62] Waters, *J. Chem. Soc.*, **1948**, 1574.

proposed that the attacking moiety in peracid oxidations is the electro-positively polarized (electrophilic) hydroxyl group $[\overset{..}{\underset{..}{O}}:H]^+$.[63, 64]   The reaction of an olefin, such as propylene, with a peracid may, therefore, be represented as follows.[10]

$$CH_3 \rightarrow \underset{\delta+}{-CH} = \underset{\delta-}{CH_2} + [\overset{..}{\underset{..}{O}}:H]^+ \rightarrow$$

$$[CH_3 \rightarrow \underset{+}{-CH} \underset{\underset{H}{\overset{..}{\underset{..}{O}:}}}{-CH_2}] \rightarrow CH_3 - CH \overset{\diagdown \diagup}{\underset{O}{}} CH_2 + H^+$$
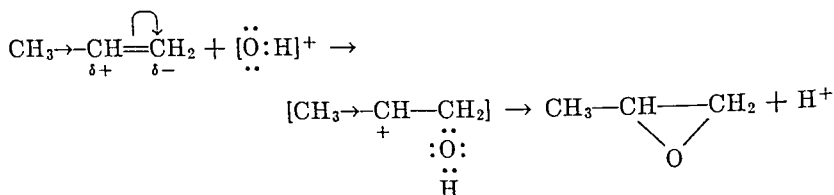
This simple formulation, however, does not account for the striking stereospecificity of the reaction which precludes a free carbonium ion intermediate.   A more reasonable alternative mechanism would involve essentially direct formation of the conjugate acid of the oxirane by donation of $[\overset{..}{O}:H]^+$ to the olefin by a peracid-general acid complex in a manner similar to that shown in the accompanying equation.   The olefin-

$$\begin{array}{c} H_3C \\ | \\ HC \quad H \quad O \\ || \diagdown | \cdots || \\ O\text{-}\text{:-}O\text{---}C\text{---}R \\ | \\ H_2C \quad HA \end{array} \rightarrow \begin{bmatrix} CH_3 \\ | \\ CH \\ \diagdown \\ OH \\ | \\ CH_2 \end{bmatrix}^+ + \begin{bmatrix} O \\ || \\ R\text{---}C\text{---}O\text{----}HA \end{bmatrix}^- \rightarrow$$

$$CH_3 - CH \overset{\diagdown \diagup}{\underset{O}{}} CH_2 + RCO_2H + HA$$
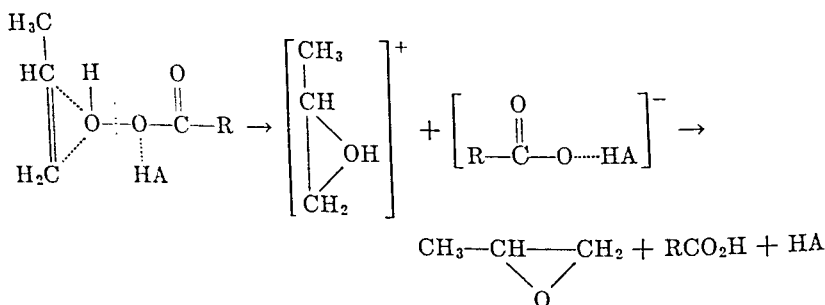
$[\overset{..}{\underset{..}{O}}:H]^+$ part of the transition state of such a process would be similar to the so-called π-complexes.[65]   This mechanism obviates any necessity for postulation of rapid and reversible $[\overset{..}{O}:H]^+$ formation from peracid and general acid (HA) followed by a slow attack of $[\overset{..}{O}:H]^+$ on the double bond.   It is also a more reasonable reaction path in the non-polar solvents often used as reaction media.

As discussed earlier (pp. 380–385) the product isolated may be the

[63] Weisenborn and Taub, *J. Am. Chem. Soc.*, **74**, 1329 (1952).
[64] Roitt and Waters, *J. Chem. Soc.*, 1949, 3060.
[65] M. J. S. Dewar, *The Electronic Theory of Organic Chemistry*, Oxford University Press, 1949.

oxirane or the hydroxy acyloxy compound, depending on the experimental conditions, the peracid used, and the stability of the oxirane.

The initial oxidation step in epoxidation and hydroxylation with organic peracids is the same, and it has generally been assumed that this reaction proceeds by *cis* addition to the double bond.[5,66] Recently, unequivocal evidence was obtained to substantiate this assumption. It was shown by x-ray diffraction and infrared absorption studies that oleic acid and oleyl alcohol (both *cis* olefins) yield *cis*-9,10-epoxystearic acid and *cis*-9,10-epoxyoctadecanol, respectively, on epoxidation with peracetic or perbenzoic acid, and the corresponding *trans* olefins, elaidic acid and elaidyl alcohol, yield *trans*-9,10-epoxystearic acid and *trans*-9,10-epoxyoctadecanol, respectively.[67]

Opening of the oxirane ring, in the preparation of α-glycols from the corresponding oxiranes, is accompanied by inversion whether the reaction is conducted in neutral, acidic, or alkaline media.[5] The only exception to this generalization apparently is the opening of an oxirane ring in the terminal position of an aliphatic chain. In this case, if the ring-opening reagent attacks the terminal position, inversion cannot occur.[68,69] A reaction scheme correlating the configurational relationships in the conversion of oleic and elaidic acids (*cis*- and *trans*-9-octadecenoic acids, respectively) to 9,10-dihydroxystearic acids by way of the intermediate oxiranes has recently been published.[5] This scheme is self-consistent and is in harmony with accepted theories of inversions, double-bond addition reactions, and the vast amount of experimental data available. This reaction sequence is undoubtedly of general applicability to other olefins with non-terminal double bonds.

It should be noted that the oxirane obtained by epoxidation of an olefin with organic peracids (*cis* addition) is identical with that obtained by hypohalogenation (*trans* addition) followed by dehydrohalogenation (inversion occurs). In the latter preparative procedure two inversions have occurred; this gives the same stereochemical result as no inversions.

Hydroxylation of olefins with potassium permanganate,[70-73] *t*-butyl hydroperoxide (osmium tetroxide catalyst),[74,75,76] or by photochemical

[66] Braun, *J. Am. Chem. Soc.*, **51**, 228 (1929).
[67] Witnauer and Swern, *J. Am. Chem. Soc.*, **72**, 3364 (1950).
[68] Abderhalden and Eichwald, *Ber.*, **48**, 1847 (1915).
[69] Sowden and Fischer, *J. Am. Chem. Soc.*, **64**, 1291 (1942).
[70] Böeseken, *Rec. trav. chim.*, **47**, 683 (1928).
[71] Böeseken and Cohen, *Rec. trav. chim.*, **47**, 839 (1928).
[72] King, *J. Chem. Soc.*, **1943**, 37.
[73] Kuhn and Ebel, *Ber.*, **58**, 919 (1925).
[74] Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).
[75] Milas and Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).
[76] Milas, Sussman, and Mason, *J. Am. Chem. Soc.*, **61**, 1844 (1939).

addition of hydrogen peroxide to the double bond [77] proceeds by *cis* addition. Catalytic hydroxylation of olefins with hydrogen peroxide and other inorganic catalysts, such as pertungstic acid, pervanadic acid, or selenium dioxide, however, proceeds by *trans* addition.[78]

SELECTION OF EXPERIMENTAL CONDITIONS

Since the oxirane group is extremely reactive and undergoes ring opening with various types of compounds which contain active hydrogen atoms, it is obvious that conditions for epoxidation must be selected with care. It is of paramount importance to avoid high reaction temperatures [1] and to exclude strongly acidic materials from the reaction mixtures [4] if high yields are to be obtained. In epoxidations with perbenzoic and monoperphthalic acids an inert solvent is employed; in epoxidations with peracetic acid, acetic acid may be used as the solvent, provided that strong acids are absent and reaction temperatures below about 30° are employed.

With unsaturated substances containing isolated double bonds, such as 2-pentene, 2-butene, oleic acid, and oleyl alcohol, epoxidation is rapid and is usually complete within eight to twenty-four hours at room temperature or below. If electron-releasing groups are attached to or are in close proximity to the ethylenic linkage, as in 2-methylpropene, 2-methyl-2-butene, and tetramethylethylene, the reaction is considerably accelerated; [10] if electron-attracting groups are attached to or are in close proximity to the ethylenic linkage, as in cinnamic, maleic, fumaric, crotonic, 2-pentenoic, and 2-hexenoic acids and their esters, the reaction is slowed down.[10] The wide range of specific reaction rates in related groups of compounds is shown most strikingly by comparing ethylene ($k \times 10^3 = 0.19$) with 2-methyl-2-butene ($k \times 10^3 =$ ca. 1000), cyclobutene ($k \times 10^3 = 21$) with 1-methylcyclopentene ($k \times 10^3 = 2200$), sorbic acid ($k \times 10^3 = 0.04$) with oleic acid ($k \times 10^3 = 384$), allylbenzene ($k \times 10^3 = 2.0$) with 1-phenyl-1-propene ($k \times 10^3 = 46$), 1,4-dihydronaphthalene ($k \times 10^3 = 37$) with 1,2-dihydronaphthalene ($k \times 10^3 = 230$–240), cinnamic acid ($k \times 10^3 = 0.13$) with cinnamyl alcohol ($k \times 10^3 = 203$), 1-phenyl-2-butene ($k \times 10^3 = 10$) with 1-phenyl-1-butene ($k \times 10^3 = 80$), eugenol ($k \times 10^3 = 2.2$) with isoeugenol ($k \times 10^3 = 127$), and safrole ($k \times 10^3 = 1.3$) with isosafrole ($k \times 10^3 = 148$).[10,73] Furthermore, the specific reaction rate of tetramethylethylene with peracetic acid at 25.8° is too high to be meas-

[77] Milas, Kurz, and Anslow, *J. Am. Chem. Soc.*, **59**, 543 (1937).
[78] Mugdan and Young, *J. Chem. Soc.*, **1949**, 2988.
[73] Swern, *Chem. Revs.*, **45**, 1 (1949).

ured.[80,81] Selected references describing kinetic studies are 2, 28, and 80-88.

The rates of oxidations with peracids can be determined readily with a minimum of experimental effort by measuring unconsumed peroxide at suitable time intervals.[11,13,89,90,91] By following the disappearance of active oxygen, the reaction can be terminated at exactly the right time, thereby minimizing side reactions and loss of active oxygen. Furthermore, the determination of unconsumed peroxide should be carried out in all peracid oxidations in which distillation techniques are employed in the recovery of solvent and in the isolation of reaction products. *In reactions which proceed slowly, a large amount of unconsumed peracid may be present in the distillation charge and cause an explosion if the peroxide is not destroyed.*

Although a wide range of conditions can be employed in the preparation of α-glycols, temperatures above 50° are undesirable because significant loss of active oxygen occurs. Early workers, who were not concerned with efficient use of active oxygen, operated at high temperatures and of necessity employed large excesses of hydrogen peroxide or peracid. Reaction temperatures below 5-10° may also be disadvantageous since they make the reaction time objectionably long.

To help in the selection of hydroxylation techniques, the methods just discussed are listed in decreasing order of efficiency and over-all desirability from the laboratory standpoint.

1. Oxidation with 30% hydrogen peroxide in formic acid solution at 40°; 1.025-1.05 moles of hydrogen peroxide per ethylenic linkage.[2,4] This method is admirably suited for the hydroxylation of isolated double bonds and is probably the best hydroxylation technique employing organic peracids. See also method 3.

2. Oxidation with 30% hydrogen peroxide in acetic acid solution containing catalytic quantities of sulfuric acid at 40°; 1.025-1.05 moles of hydrogen peroxide per ethylenic linkage.[2,4]

[80] Böeseken and Stuurman, *Proc. Acad. Sci. Amsterdam*, 39, 2 (1936) [C. A., 30, 3304 (1936)].
[81] Böeseken and Stuurman, *Rec. trav. chim.*, 56, 1034 (1937).
[82] Bodendorf, *Arch. Pharm.*, 268, 491 (1930).
[83] Böeseken and Blumberger, *Rec. trav. chim.*, 44, 90 (1925).
[84] Böeseken and Hanegraaff, *Rec. trav. chim.*, 61, 69 (1942).
[85] Heinänen, *Ann. Acad. Sci. Fennicae*, A59, No. 13, 3 (1943) [C. A., 41, 2307 (1947)].
[86] Smit, *Rec. trav. chim.*, 49, 686 (1930).
[87] Stuurman, *Proc. Acad. Sci. Amsterdam*, 38, 450 (1935) [C. A., 29, 4657 (1935)].
[88] J. Stuurman, thesis, University of Delft, 1936.
[89] Kolthoff and Menzel, *Die Massanalyse*, Vol. II, 2nd ed., p. 413, Springer, Berlin, 1931.
[90] Marks and Morrell, *Analyst*, 54, 503 (1929).
[91] Wheeler, *Oil and Soap*, 9, 89 (1932).

3. The same as 1 and 2, but employing 90% hydrogen peroxide.[48, 55] Although slightly more complete reaction is obtained with 90% hydrogen peroxide, the hazards attendant upon its use make it less desirable for laboratory investigation.[92, 93, 94] By use of the more concentrated peracids, however, ethylenic linkages adjacent to carboxyl groups can be hydroxylated readily.[55]

4. Prior preparation of performic or peracetic acids and employment of the peracids under conditions similar to 1, 2, and 3 above.

5. Epoxidation with peracetic, perbenzoic, or monoperphthalic acid, followed by hydrolysis. The only virtue of this technique, probably, is that one can obtain either the oxirane or the α-glycol from a given unsaturated substance.

Because of the instability of performic acid, there is usually little point in its separate preparation (method 4). If it is prepared separately, however, it should be used immediately. Performic acid of 90% strength is highly explosive.[94a] In contrast to performic acid, peracetic acid is relatively stable and can be stored conveniently. In the absence of catalysts, concentrated solutions of peracetic acid are fairly stable at room temperature (15–25°); 87–95% solutions remain virtually unchanged on standing for about five weeks,[46] the 50% solution shows no loss of peracid after storage for two weeks,[46] and the 45% solution retains 75% of the peracid after seven weeks.[47] The 45% solution retains 94% of the peracid after seven weeks of storage if it is stabilized with sodium pyrophosphate[47] (other stabilizers have also been suggested).[95, 96] Five to ten per cent solutions of peracetic acid in acetic acid, however, show significant losses of active oxygen at room temperature but little loss at 0 to 5°.[1] Although peracetic acid can be prepared by efficient processes and only a small amount of active oxygen is lost or unavailable for oxidative purposes, the separate preparation of the peracid is a time-consuming step in the hydroxylation reaction, and method 2 is more desirable. Concentrated solutions of peracetic acid have recently become commercially available.[97]

There is a wide variety of methods for preparing organic peracids, and many solvents have been suggested for use in their preparation, isolation, and application as oxidizing agents. This phase of peracid chemistry is

[46] Bellinger, Friedman, Bauer, Eastes, and Bull, *Ind. Eng. Chem.*, **38**, 310 (1946).
[47] Bellinger, Friedman, Bauer, Eastes, and Edmonds, *Ind. Eng. Chem.*, **38**, 627 (1946).
[94] Shanley and Greenspan, *Ind. Eng. Chem.*, **39**, 1536 (1947).
[94a] Weingartshofer-Olmos and Giguère, *Chem. Eng. News*, **30**, 3041 (1952).
[95] Naamlooze Vennootschap Industrieele Maatschappij Voorheen Noury and Van Der Lande and Van Der Lande, Brit. pat. 234,163 [*C. A.*, **20**, 768 (1926)].
[96] Reichert, McNeight, and Elston, U. S. pat. 2,347,434 [*C. A.*, **39**, 89 (1945)].
[97] Buffalo Electrochemical Co., *Peracetic Acid Data Sheet* 1 (1947).

not sufficiently pertinent to be discussed here in detail, but information has recently been published on this subject.[79] The particular oxidative method and solvent selected will depend, in large part, on the solubility of the peracid and on the structure of the unsaturated substance and the oxidation products. Furthermore, the stability of the peracid and the oxidation products in the solvent medium and the ease of separation of the desired products from the other materials present have an important bearing on the selection of reaction conditions. The solvent has been reported to affect the rates of decomposition of peracids as well as their rates of reaction with unsaturated substances.[7, 13, 83, 98–101]

For information regarding other organic peracids (properties, methods of preparation, special techniques, etc.) reference 79 can be consulted.

EXPERIMENTAL PROCEDURES

Caution. *All preparations of and reactions with organic peracids should be conducted behind a safety shield, because a reaction occasionally proceeds with uncontrollable violence.* When an olefin of unknown structure or one that contains at least three electron-releasing groups attached to or in close proximity to the ethylenic linkage is epoxidized or hydroxylated for the first time, the reaction should be run on a small scale (preferably 0.1 mole or less), and provision should be made for efficient cooling. Detailed information regarding the properties of concentrated hydrogen peroxide [92, 93, 94, 102–105] and organic peracids [79] has recently been published.

Peracid oxidation mixtures should not be distilled unless an analysis has indicated the absence or low concentration of active oxygen. When the peracid content is low, acetic and formic acids can be safely and completely distilled from oxidation reactions at or below room temperature by the use of low pressure. Peracids and other peroxides can be conveniently destroyed by the addition of ferrous sulfate, sodium bisulfite, or other reducing agents.

[98] Berezovskaya and Semikhatova, *Bull. acad. sci. U.R.S.S., Classe sci. math. nat.*, 1934, 1583, 1589 [*C. A.*, **29**, 6130 (1935)].
[99] Calderwood and Lane, *J. Phys. Chem.*, **45**, 108 (1941).
[100] Lagrave, *Ann. Chim.*, [10] **8**, 363 (1927).
[101] Meerwein, Ogait, Prang, and Serini, *J. prakt. Chem.*, **113**, 9 (1926).
[102] Bretschger and Shanley, *Trans. Electrochem. Soc.*, **92**, 10 pp. (1947) preprint.
[103] McKee, *Mech. Eng.*, **68**, 1045 (1946).
[104] Médard, *Compt. rend.*, **222**, 1491 (1946).
[105] Schumb, *Ind. Eng. Chem.*, **41**, 992 (1949).

Analysis of Peracids

Perbenzoic Acid. Perbenzoic acid in an organic solvent can be determined iodimetrically by shaking the solution with an aqueous acetic acid solution of potassium iodide. A known volume of the perbenzoic acid solution is pipetted into an iodine flask containing 50 ml. of 0.4 N acetic acid and 1 g. of potassium iodide, the mixture is shaken, and the liberated iodine is titrated with 0.05–0.1 N sodium thiosulfate solution, starch indicator being used.

In following the course of the oxidation of water-insoluble substances which precipitate upon addition of the solution to the aqueous acetic acid, a sharper end point is obtained by adding the perbenzoic acid solution to 25 ml. of a chloroform-acetic acid solution (3:2 by volume). Two milliliters of saturated potassium iodide solution is added, and the mixture is allowed to stand for five minutes. Seventy-five milliliters of water is added, the solution is shaken, and the liberated iodine is titrated with 0.05–0.1 N sodium thiosulfate.[91] One milliliter of 0.1 N sodium thiosulfate is equivalent to 0.00690 g. of perbenzoic acid.

Monoperphthalic Acid. Monoperphthalic acid can be determined by the same methods employed for perbenzoic acid. An alternative procedure [106] is to add 2 ml. of the solution to 30 ml. of 20% aqueous potassium iodide and titrate the liberated iodine after 10 minutes with 0.05 N sodium thiosulfate solution. One milliliter of 0.05 N sodium thiosulfate is equivalent to 0.00455 g. of monoperphthalic acid.

Peracetic Acid. The peroxide components in the peracetic acid solutions described below are determined on a single sample as follows:[44,45] 0.2–2 ml. of the solution (accurately dispensed from a pipette or weighed) is diluted with 50 ml. of 4 N aqueous sulfuric acid which has been cooled to 0°. This solution is titrated rapidly with 0.1 N potassium permanganate to a pink end point. This determines unreacted hydrogen peroxide; 1 ml. of 0.1 N potassium permanganate is equivalent to 0.00170 g. of hydrogen peroxide. The peracetic acid is determined by adding 2 ml. of saturated aqueous potassium iodide to the same solution and rapidly titrating with 0.1 N sodium thiosulfate, starch indicator being used; 1 ml. of 0.1 N sodium thiosulfate is equivalent to 0.00380 g. of peracetic acid. At this point, the flask and its contents are heated on the steam bath for five to ten minutes, causing a return of the blue color, and liberated iodine is titrated with 0.1 N sodium thiosulfate. The last titration gives the diacetyl peroxide content; 1 ml. of 0.1 N sodium thiosulfate is equivalent to 0.00590 g. of diacetyl peroxide. It

[106] Böhme, *Org. Syntheses*, **20**, 70 (1940).

has been reported that ceric sulfate is more satisfactory than potassium permanganate for determination of residual hydrogen peroxide.[107]

In following the consumption of active oxygen during the oxidation of water-insoluble substances with peracetic acid, the procedure described under the analysis of perbenzoic acid should be employed.[91] This determines total active oxygen and not peracetic acid alone, but the difference between the titrations at succeeding time intervals gives a measure of peracetic acid consumed.

Performic Acid. The procedures described in the analysis of peracetic acid are used.

Preparation of Peracids

Perbenzoic Acid (Benzoyl Peroxide-Sodium Methoxide Method). Directions published in *Organic Syntheses*[11] are probably the most satisfactory for preparing stable solutions of perbenzoic acid. Briefly, this method consists in (a) allowing benzoyl peroxide to react with sodium methoxide in chloroform-methanol solution, (b) extracting the sodium perbenzoate solution with water, (c) acidifying with sulfuric acid, and (d) extracting the perbenzoic acid with chloroform. Yields of perbenzoic acid of about 85% are obtained. *Do not recrystallize benzoyl peroxide from hot chloroform, as suggested in the original* Organic Syntheses *procedure, as this operation is hazardous.* Benzoyl peroxide may be purified safely by adding methanol to a chloroform solution of the peroxide at room temperature.[108] A recrystallized grade is commercially available.[109]

For preparation of large quantities of perbenzoic acid or solutions which are to be stored for a long time, a modified procedure has been recommended.[13]

(a) The mixture is kept below 0° during the addition of the chloroform solution of benzoyl peroxide to the methanol solution of sodium methoxide. Since this reaction is highly exothermic, a large quantity of salt-ice freezing mixture at −15° is employed to cool the reaction flask, the benzoyl peroxide solution is added at a slow, even rate of about 15–20 ml. per minute, and the reaction flask is swirled vigorously and continuously during the addition. There is no need to wait four to five minutes, as specified in the original procedure[11] before extracting the mixture with water.

(b) Instead of transferring the chloroform-methanol solution containing sodium perbenzoate to a separatory funnel, about 150 ml. of

[107] Greenspan and MacKellar, *Anal. Chem.*, **20**, 1061 (1948).
[108] Nozaki and Bartlett, *J. Am. Chem. Soc.*, **68**, 1686 (1946).
[109] Lucidol Corporation, Buffalo, New York.

water containing chopped ice is added to the reaction mixture which is rapidly swirled. The mixture is then transferred to the separatory funnel, and 350 ml. of water containing chopped ice is added to the rapidly swirled material. In this way, the formation of lumps which dissolve slowly is prevented.

(c) The emulsion that collects at the interface of the aqueous sodium perbenzoate phase and the chloroform phase is discarded. Only three to five minutes is allowed for separation of the phases. Likewise, emulsions formed during the washing of the aqueous layer are discarded.

(d) The aqueous phase is washed with two 100-ml. portions of carbon tetrachloride, instead of chloroform.

(e) After acidification, the aqueous solution is extracted with reagent-grade benzene rather than chloroform. At this point, the temperature of the solution should be above 5°, to prevent freezing of the benzene.

(f) The benzene solution is washed with water, dried over anhydrous sodium sulfate (calcium chloride sometimes causes a sudden decomposition of the peracid [11]), and stored in the dark at about 10° until used.

Crystalline perbenzoic acid can be obtained by removal of the solvent under vacuum, as described in *Organic Syntheses*,[11] and purified by recrystallization from chloroform-ethanol mixtures [110] or from petroleum ether.[111] Perbenzoic acid melts at about 41° and is soluble in the common organic solvents, except cold petroleum ether.

Perbenzoic Acid (Benzaldehyde-Air Method).[3] The air oxidation of benzaldehyde in acetone solution irradiated with ultraviolet light is a convenient method for the preparation of moderately large quantities of perbenzoic acid.

In a 5-l. three-necked Pyrex flask equipped with a thermometer, a solid carbon dioxide-cooled reflux condenser, and two fritted glass disks reaching to the bottom of the flask, 520 g. (4.9 moles) of freshly distilled benzaldehyde is dissolved in 4 l. of acetone. The flask is immersed in an ice-water bath and irradiated from the top with three 125-watt Hanovia quartz mercury-vapor lamps, symmetrically placed around the flask, while a rapid stream of dry air is passed through the fritted disks and into the solution for twenty-four hours at 5–10°. The reaction is conducted in a fume hood because of the formation of ozone. If the reaction cannot be run without interruption, the acetone solution can be stored at 5–10° with little or no loss of perbenzoic acid. After about twenty-four hours, the rate of peracid formation decreases considerably

[110] Maan, *Rec. trav. chim.*, **48**, 332 (1929).

[111] Baeyer and Villiger, *Ber.*, **33**, 1569 (1900).

and the solution then contains about 2 moles of perbenzoic acid. The yield is 40–45%.

Monoperphthalic Acid. The procedure described in *Organic Syntheses*,[106] consisting in the reaction of phthalic anhydride with alkaline 30% aqueous hydrogen peroxide, is satisfactory, and gives 65–70% yields. It has been reported to be advantageous to employ 40% sodium hydroxide solution and to add crushed ice directly to the reaction mixture.[112] In this procedure, the peracid is extracted with ether, but, if ether is not a suitable solvent for the subsequent oxidation reactions, it can be removed readily and replaced by dioxane or other solvent by a procedure described in *Organic Syntheses*.[106]

Peracetic Acid.[1, 47] In a 5-l. three-necked flask equipped with a mechanically driven glass stirrer, a thermometer, and a separatory funnel is placed 2250 g. of acetic anhydride, which has been filtered through glass wool to remove particles which may catalyze peroxide decomposition. The thermometer should be immersed in the liquid, and at least one neck of the flask should be open to the atmosphere. The acetic anhydride is warmed to 35–40° in a water bath into which cold or warm water can be run at will and removed rapidly if necessary. By means of the separatory funnel, 500 g. of 25–30% hydrogen peroxide is added in about one hour with agitation, the temperature being maintained at 40°. The reaction becomes mildly exothermic soon after the addition of hydrogen peroxide is started, and cooling is required for three to four hours after the addition is complete to maintain the temperature at 40° (bath temperature 25–30°). The solution is allowed to stand overnight at room temperature. The concentration of peracetic acid is then about 0.8–1.2 M (6–9%). The yield is 60–90%. The solution contains diacetyl peroxide and some unconverted hydrogen peroxide in addition to peracetic acid and acetic acid.

A concentrated solution of peracetic acid [47] is prepared by cautiously adding 9.1 g. of 90% hydrogen peroxide to a stirred solution of 10 g. of acetic acid and 0.11 ml. of concentrated sulfuric acid contained in a flask immersed in a water bath at 22–23°. At the end of four hours, the peracetic acid content of the solution is about 44%; it rises to a maximum of 46% within twelve to fifteen hours.

Performic Acid.[47, 53, 54] In a 500-ml. Erlenmeyer flask, 25 g. of 25–30% hydrogen peroxide and 250 g. of 98–100% formic acid are mixed at room temperature. Since the reaction is only mildly exothermic (temperature rise 1–2°), no cooling is required in batches of this size. The maximum content of performic acid (approximately 5%) is obtained within thirty

[112] Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

to sixty minutes, as determined by the analytical techniques already described.

A concentrated solution of performic acid is prepared by cautiously adding 28.4 g. of 90% hydrogen peroxide to a stirred solution of 23.0 g. of 98–100% formic acid and 0.28 ml. of concentrated sulfuric acid contained in a flask immersed in a water bath at 22–23°.[47, 55] Maximum performic acid concentration (approximately 35%) is reached within thirty minutes.

Performic acid solutions are unstable, and active oxygen is lost at a fairly rapid rate (several per cent per hour at room temperature); the solutions, therefore, should not be stored but should be used immediately.

Epoxidation with Perbenzoic Acid

1,2-Epoxyethylbenzene (Styrene Oxide).[12, 113]   To a solution of 42 g. (0.30 mole) of perbenzoic acid in 500 ml. of chloroform, prepared as described on p. 393, 30 g. (0.29 mole) of styrene is added. The solution is maintained at 0° for twenty-four hours, with frequent shaking during the first hour. At the end of twenty-four hours titration of an aliquot part of the solution shows that only the slight excess of perbenzoic acid remains. The benzoic acid is removed from the chloroform solution by shaking with several portions of 10% sodium hydroxide solution, the alkali is removed by washing with water, and the chloroform solution is dried over anhydrous sodium sulfate. Fractional distillation yields 24–26 g. (69–75%) of 1,2-epoxyethylbenzene, b.p. 101°/40 mm., as an almost colorless liquid.

cis-9,10-Epoxystearic Acid.[3, 30]   To 750 ml. of an acetone solution of 0.4 mole of perbenzoic acid, prepared as described on p. 394, 85 g. (0.3 mole) of oleic acid [114, 115, 116] is added at 0–5°. The solution is allowed to stand for forty hours at room temperature and then cooled to −25° and filtered; the precipitate is washed once with cold acetone. The crude 9,10-epoxystearic acid (purity 95–99%) is a white powder weighing about 85 g. Two recrystallizations from acetone at 0 to −25° yields 55–60 g. of analytically pure *cis*-9,10-epoxystearic acid, m.p. 59.5–59.8°. Oxirane oxygen: [117] calcd., 5.36%; found, 5.33–5.37%. The yield is 62–67%.

[113] Hibbert and Burt, *Org. Syntheses*, **8**, 102 (1928); *Coll. Vol.* I, 494 (1941).
[114] Brown and Shinowara, *J. Am. Chem. Soc.*, **59**, 6 (1937).
[115] Swern, Knight, and Findley, *Oil and Soap*, **21**, 1 (1944).
[116] Wheeler and Riemenschneider, *Oil and Soap*, **16**, 207 (1939).
[117] Swern, Findley, Billen, and Scanlan, *Anal. Chem.*, **19**, 414 (1947).

1,2-Epoxy-2-methyl-3-butene (Isoprene Monoxide) (preferential oxidation of one ethylenic linkage in a conjugated diene).[118] To a stirred solution of 16 g. (0.235 mole) of isoprene in 50 ml. of ethyl chloride cooled in an ice bath a cold solution of 30 g. (0.217 mole) of perbenzoic acid in 150 ml. of ethyl chloride is added from a dropping funnel. The contents of the flask and dropping funnel are protected from moisture by drying tubes. After the perbenzoic acid solution has been added, the reaction flask is allowed to stand in a refrigerator until the oxidizing agent is completely consumed (approximately twenty-four hours). The solution is then shaken cautiously with double the calculated quantity of sodium bicarbonate solution (30 g. per 100 ml. of water) in a cooled separatory funnel until evolution of carbon dioxide ceases. The aqueous layer is discarded, and the ethyl chloride solution is dried overnight in a refrigerator with anhydrous sodium sulfate. The solution is filtered, and the filtrate is distilled through a Widmer column until unreacted isoprene begins to distill. The residual material is then fractionated twice and yields 7 g. (30–40%) of 1,2-epoxy-2-methyl-3-butene (isoprene monoxide).

Epoxidation with Monoperphthalic Acid

β- and α-Cholesteryl Oxide Acetates.[25] A solution of 10 g. (0.023 mole) of cholesteryl acetate, m.p. 112–114°, in 50 ml. of ether is mixed with 266 ml. of an ether solution containing 8.4 g. (0.046 mole) of monoperphthalic acid. The solution is refluxed for six hours, and the solvent is removed by distillation. The residue is dried under reduced pressure and digested with 250 ml. of chloroform which has been dried over anhydrous potassium carbonate. The mixture is filtered, yielding 6.7 g. of phthalic acid (87% recovery) and a colorless solution, from which the solvent is removed under reduced pressure. The residue is crystallized from 30 ml. of methanol, giving 6.0 g. (58% yield) of β-cholesteryl oxide acetate, which on recrystallization gives the pure product, m.p. 111–112°, $[\alpha]_D^{25} - 21.8°$. Concentration of the filtrate gives 1.55 g. (15% yield) of α-cholesteryl oxide acetate. The α-isomer, purified by crystallization from ethanol, has a m.p. of 101–103°, $[\alpha]_D^{25} - 44.6°$.

Hydroxylation with Hydrogen Peroxide-Acetic Acid

9,10-Dihydroxystearic Acid (High-Melting Isomer).[4] A well-stirred solution consisting of 270 g. (0.898 mole) of elaidic acid (containing 94% of elaidic acid and 6% of saturated acids), 810 ml. of glacial acetic

118 Pummerer and Reindel, *Ber.*, 66, 335 (1933).

acid, and 20 g. of concentrated sulfuric acid is heated to 40°, and 123 g. of 25.5% hydrogen peroxide (0.925 mole) is added dropwise over a period of fifteen minutes. The reaction is only slightly exothermic. A granular precipitate begins to form after about thirty minutes and increases in bulk as the oxidation proceeds. The total reaction time at 40° is five hours. The reaction mixture is then poured into several volumes of hot water (95–100°) and stirred well for several minutes. The mixture is cooled to room temperature and filtered, and the precipitate is washed well with cold water. The product, which weighs about 300 g. and consists of a mixture of 9,10-dihydroxystearic acid and hydroxyacetoxystearic acids, is heated at 100° for one hour with an excess of 2 N sodium hydroxide and then poured into excess hydrochloric acid, with stirring. The granular precipitate is filtered and washed free of acid. It weighs about 280 g. (93%) and consists of somewhat impure 9,10-dihydroxystearic acid, m.p. 125–128°. Crystallization from 95% ethanol (7 ml./g.) at 0–5° yields 220 g. (78%) of pure 9,10-dihydroxystearic acid as glistening plates, m.p. 130–131°.

Hydroxylation with Hydrogen Peroxide-Formic Acid

9,10-Dihydroxystearic Acid (Low-Melting Isomer).[4] To a well-stirred solution of 141 g. (0.5 mole) of oleic acid [114,115,116] in 423 ml. of 98–100% formic acid in a 1-l. three-necked flask at 25° is added during a fifteen-minute period 59 g. of 30% (100 volume) hydrogen peroxide solution (17.5 g.; 0.513 mole; 2.5% excess of hydrogen peroxide). The reaction becomes vigorously exothermic after five to ten minutes and the mixture becomes homogeneous in twenty to thirty minutes after all the hydrogen peroxide has been added. The temperature is kept at 40° with a cold-water bath at the start and a warm-water bath toward the end of the reaction. After about two hours no further consumption of peroxide is observed, and the formic acid is removed by distillation under reduced pressure (b.p. 50°/125 mm.) in a stream of carbon dioxide or nitrogen to prevent bumping. The residue in the flask, which consists of hydroxyformoxystearic acids, is heated for one hour at 100° with an excess of 3 N aqueous sodium hydroxide, and the hot, pale yellow solution is slowly poured into an excess of 3 N hydrochloric acid with stirring. The oil, which separates, is allowed to solidify, and the aqueous layer is discarded. The white solid is remelted with hot water on a steam bath and stirred well to remove residual salts and water-soluble acids. When the oil has resolidified, the aqueous layer is discarded, and the solid is broken into small pieces and air dried. This product consists of fairly pure 9,10-dihydroxystearic acid (iodine

number about 2–4, neutralization equivalent 315–320), weighs about 150–155 g. (97–99%), and melts at about 92°. The small quantity of unsaturated material present can be separated readily by grinding the material and washing it by decantation with several portions of petroleum naphtha (hexane fraction, boiling range 63–70°). 9,10-Dihydroxystearic acid, m.p. 93° and iodine number 0.0, is obtained from the crude product with a loss of about 6%. In order to obtain an analytically pure product, the dihydroxystearic acid is recrystallized from 95% ethanol, yielding 9,10-dihydroxystearic acid, m.p. 95°, in 80% overall yield.

If purified oleic acid is not available, red oil (commercial product containing about 60–75% oleic acid) may be employed. The crude 9,10-dihydroxystearic acid obtained from this material melts at about 70–75° (compared to 92° when pure oleic acid is used), and several recrystallizations from 95% ethanol are required to obtain a pure product. The yield of 9,10-dihydroxystearic acid from red oil is about 50–60% of the available oleic acid. Furthermore, the 90% grade of formic acid is satisfactory, but the reaction mixture remains heterogeneous throughout. In preparations one-tenth the size described, the 25–30% hydrogen peroxide can be added in one portion. In larger preparations the addition may require thirty minutes to one hour. In preparations five to ten times the size described, it is more convenient to pour the reaction mixture into a large volume of water and then hydrolyze the washed oily layer of hydroxyformates as described.

When 90% hydrogen peroxide is employed instead of the 30% grade, the crude dihydroxystearic acid has an iodine number of 1, instead of 2–4. With the concentrated peroxide, the quantity of formic acid can be reduced to about one-seventh the amount employed with 25–30% hydrogen peroxide.

1,2-Tetradecanediol.[2] To a well-stirred mixture of 49.2 g. (0.25 mole) of 1-tetradecene, b.p. 158–159°/60 mm., n_D^{20} 1.4357 (prepared by efficient fractional distillation of the 95% commercial grade), and 295 ml. of 98–100% formic acid at 25°, 35 g. of 25.6% hydrogen peroxide (0.263 mole; 5% excess) is added in one portion. The mixture is heated and stirred for about twenty-four hours at 40°, or until an analysis[91] indicates that the theoretical quantity of peroxide has disappeared. The reaction mixture is heterogeneous throughout. The formic acid is recovered under reduced pressure, and the distillation residue is refluxed for one hour with excess 3 N ethanolic potassium hydroxide. Most of the ethanol is then evaporated on the steam bath, and a large quantity of hot water is added, precipitating the glycol as an oil. When the glycol has solidified, the water layer is siphoned off, and the product is remelted

with hot water and allowed to resolidify. The combined water washes are extracted with ether to remove a small quantity of dissolved glycol, and the residue obtained after evaporation of the ether is combined with the main portion of glycol. The crude glycol is broken up into small pieces and air dried, yielding about 55 g. (95%) of fairly pure 1,2-tetradecanediol, m.p. about 65°; iodine number about 4. This is recrystallized from methanol (8 ml./g.) at 0°, yielding about 40 g. (69%) of pure product, m.p. 68–68.5°.

trans-1,2-Cyclohexanediol.[55] To a mixture of 105 g. of 98–100% formic acid and 13 g. (0.115 mole) of 30% hydrogen peroxide, 8.0 g. (0.097 mole) of cyclohexene is added. The immiscible layers are shaken together briefly; spontaneous heating occurs, and the suspension becomes homogeneous at 65–70°, where it is held for two hours on the steam bath. Most of the formic acid is removed by distillation, and the residue is heated on the steam bath for forty-five minutes with 50 ml. of 20% sodium hydroxide. After cooling, the yellow solution is neutralized with hydrochloric acid and evaporated to dryness under vacuum. The resulting solid is distilled, yielding 10.25 g. of a fraction, b.p. 128–132°/15 mm., which solidifies immediately. Recrystallization from acetone gives 7.9 g. (70%) of *trans*-1,2-cyclohexanediol, m.p. 102–103°. A larger scale oxidation of cyclohexene is described in *Organic Syntheses*.[119]

Hydroxylation with Performic Acid

2,3-Dihydroxynonanoic Acid.[55] Twenty grams (0.13 mole) of 2-nonenoic acid is added slowly to a well-stirred solution of performic acid prepared by the reaction of 69 g. of 98–100% formic acid, 19 g. (0.5 mole) of 90% hydrogen peroxide, and 0.50 g. of concentrated sulfuric acid. The emulsified mixture is heated to 55–60° to start the reaction and is then held at this temperature for two hours while stirring is continued. The temperature is then allowed to rise to 95° until the spontaneous reaction is over (twenty-five minutes) and the excess peracid largely destroyed. Most of the formic acid is removed by vacuum distillation, and the residue is saponified on the steam bath for one-half hour with 175 ml. of 10% sodium hydroxide. After acidification with hydrochloric acid, the oily product is extracted with ether and the extract is dried over anhydrous sodium sulfate. Evaporation of the ether yields a waxy solid which is suspended in benzene and filtered, yielding 2,3-dihydroxynonanoic acid as white slippery flakes. Concentration of the filtrate followed by addition of ligroin gives two additional crops,

[119] Roebuck and Adkins, *Org. Syntheses*, **28**, 35 (1945).

the total yield of product being 12.4 g. (51%). On crystallization from ethyl acetate or water, pure 2,3-dihydroxynonanoic acid, m.p. 118–118.5°, is obtained.

TABLE OF ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

The following table lists the ethylenic compounds which have been epoxidized or hydroxylated with organic peracids. The table is divided into the following sections: A, Hydrocarbons and substituted hydrocarbons; B, Steroids (alphabetical order); C, Acids; D, Alcohols; E, Esters; F, Aldehydes and ketones (including carbohydrates); G, Ethers; H, Miscellaneous.

In the preparation of the table the literature has been consulted to October 1951. The addendum to Table I lists the compounds whose epoxidation or hydroxylation with organic peracids was reported from October 1, 1951, to October 1, 1952.

TABLE I

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

| Ethylene Compound | | Yield of Oxirane, % (Reference) | | | Yield of α-Glycol, % (Reference) | | |
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
	A. Hydrocarbons and Substituted Hydrocarbons						
C_2H_4	Ethylene-C14	30–53 (120)				73 (122)	
C_4H_6	1,3-Butadiene	42 (118, 121)				Low (123)	
$C_4H_6Br_2$	1,4-Dibromo-2-butene					30 (123)	
$C_4H_6Cl_2$	1,4-Dichloro-2-butene					— (123)	
	3,4-Dichloro-1-butene				70 (124)		
C_4H_7Cl	3-Chloro-2-methyl-1-propene (methallyl chloride)					— (122)	
C_4H_8	1-Butene					85 (122)	
	2-Butene				54 (71)		
C_5H_7Cl	1-Chloro-1-cyclopentene	75–80 (125, 126)					
	1-Chloro-2-cyclopentene	75–80 (125, 126)					
C_5H_8	Cyclopentene	80–90 (70, 127)			— (129)		
	Isoprene	30–60 (118, 121, 128)			— (129)		
	3-Methyl-1,2-butadiene			— (23)			
	1,4-Pentadiene	— (121)					
C_5H_{10}	Amylenes	— (130)					
C_6H_7N	1-Cyano-2-cyclopentene	85–90 (131)					
C_6H_8	1,3-Cyclohexadiene	75–80 (125, 126, 132, 133)					
C_6H_9Cl	1-Chloro-1-cyclohexene	75–80 (125, 126, 134)					
	1-Chloro-2-cyclohexene	75–80 (125, 126, 134)					

Formula	Compound	Yield (%) (References)				
C₆H₁₀	Biallyl	— (135)				
	Cyclohexene	100 (70, 136)	60-67 (32, 137)	03-100 (32, 70, 138, 139, 140)	05-75 (55, 110, 122, 141)	30 (142)
	2,3-Dimethylbutadiene	— (121)				
	1,5-Hexadiene	66 (121, 143)				
	2,4-Hexadiene	— (121)			53 (141, 144)	
	1-Methyl-1-cyclopentene	75 (10, 70, 144)				
	3-Methyl-1-cyclopentene	— (132)			65 (141)	
	4-Methyl-1-cyclopentene	— (132)			70 (144)	
	5-Methyl-1-cyclopentene					
	5-Methylcyclopentenes (mixture of isomers)					
C₆H₁₁BrO	4-Methoxy-5-bromo-1-pentene	85 (145, 146)				
C₆H₁₂	2,3-Dimethyl-2-butene	— (7)		— (147)		
	2-Methyl-2-pentene	03 (148)	— (149)			
C₆H₁₂O	2-Methyl-4-methoxy-1-butene	— (130)				
C₆H₉N	3-Cyano-1-cyclohexene					
C₆H₁₀O	2-Methyl-2,5-hexadien-4-one	— (126)				
C₇H₁₁Cl	2-Chloro-1-methyl-1-cyclohexene	75-80 (125, 126, 134)				
	2-Chloro-4-methyl-1-cyclohexene	— (150, 151)				
	2-Chloro-1-methylenecyclohexane	100 (152)				
C₇H₁₂	Cycloheptene			— (140)	59 (141)	
	2,3-Dimethyl-1-cyclopentene	— (121)			30 (141)	
	3-Ethyl-1-cyclopentene	50-75 (10, 70, 136, 153)				
	1,6-Heptadiene				73 (141)	
	1-Methyl-1-cyclohexene	55 (132, 136, 154)				
	4-Methyl-1-cyclohexene	60-90 (136, 155)			81 (141)	
	6-Methyl-1-cyclohexene	— (132)			40 (141)	
	3-Methyl-1-methylenecyclopentane	— (150)				
	Methylenecyclohexane	70 (125)				
C₇H₁₂O	1-Ethoxy-1-cyclopentene	31 (157)				
C₇H₁₃Cl	1-Chloro-1-heptene	— (158)		— (129)		
C₇H₁₄	1-Heptene	— (158)		— (129)		
	5-Methyl-1-hexene	— (158)				
	3-Heptene	— (159)				

TABLE I—*Continued*

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
		A. Hydrocarbons and Substituted Hydrocarbons—Continued					
C_8H_8	Cyclooctatetraene	40–60 (160, 100a)			55 (101)		
	Styrene	69–75 (12, 22, 113, 162, 163, 164)				40 (122)	
$C_8H_8Br_2Cl_2$	7,8-Dichlorobicyclo-[4.2.0]-dibromo-octene	— (160)					
$C_8H_8Cl_2$	7,8-Dichlorobicyclo-[4.2.0]-2,4-octadiene	— (160)					
C_8H_{12}	1-Vinylcyclohexene	— (121)					
	4-Vinylcyclohexene			— (165)	69–80 (165a)		
C_8H_{14}	Cyclooctene	65 (160)					
	1,2-Dimethyl-1-cyclohexene	75 (166)					
	1,3-Dimethyl-1-cyclohexene	— (132)					
	2,4-Dimethyl-1-cyclohexene	— (132)					
	Dimethylcyclohexene	— (7)					
	2,5-Dimethyl-1,5-hexadiene	— (121)					
	3-Methyl-1-methylenecyclohexane	— (132)					
	1-n-Propyl-1-cyclopentene	— (132)					
	1-Isopropyl-1-cyclopentene	— (132)					
	1,7-Octadiene	— (121)					
$C_8H_{14}O$	1-Ethoxy-1-cyclohexene	70 (125)					
	3-Ethoxy-1-cyclohexene	— (155, 167)					
$C_8H_{15}Cl$	2-Chloro-2-octene	25 (157)					
C_8H_{16}	Diisobutylene	— (6, 7)		— (41, 43, 168)			
	2-Methyl-1-heptene			— (129)			

Note: the following table is printed sideways (landscape) on the page. Columns A–E below correspond to the several unlabelled data columns reading from the one nearest the compound names (A) outward to the farthest (E).

Molecular formula	Compound	A	B	C	D	E
	1-Octene	15 (21)	35 (2)		58–70 (2, 169)	
	Octenes	40 (36)	28 (21)	— (36, 40, 147)	— (36)	
	2,4,4-Trimethyl-1-pentene	70 (40)	— (36, 40)	— (36, 40, 147)	40 (40)	
	2,4,4-Trimethyl-2-pentene	25 (170)	— (36, 40)			
$C_8H_{16}O_2$	1,1-Diethoxy-2-butene	100 (70, 132, 163, 171)		100 (138)		
C_9H_8	Indene	— (172)				
C_9H_9Br	3-(p-Bromophenyl)-1-propene	80 (172)				
	1-(p-Bromophenyl)-1-propene	— (170)				
C_9H_9Cl	3-Chloro-1-phenyl-1-propene	60–80 (173, 174)				
C_9H_{10}	Allylbenzene	80 (162, 175, 176)		100 (138)		
	1-Phenyl-1-propene	80 (162, 177)				
	2-Phenylpropene					— (178)
C_9H_{14}	Hexahydroindene	— (132)				
C_9H_{16}	4-Methyl-2-ethylcyclohexene	— (132, 179, 180)				
	3-Methyl-1-ethylidenecyclohexane	— (121)				
	1,8-Nonadiene	— (132)				
	1-n-Propyl-1-cyclohexene	— (132)				
	1-Isopropyl-1-cyclohexene	100 (181)				
C_9H_{18}	1-Nonene			— (168)		
	Iceonone	70 (127, 171)				
$C_{10}H_{10}$	Dicyclopentadiene	— (182)				
	1,2-Dihydronaphthalene	— (163)				
	2,3-Dihydronaphthalene	— (163, 182)				
	1,4-Dihydronaphthalene	— (121)				
	Divinylbenzene	— (183)		100 (139)		(183)
	cis-1-Phenyl-1,3-butadiene	75 (172)				
$C_{10}H_{11}Br$	1-(p-Bromophenyl)-1-butene	75 (172)				
	4-(p-Bromophenyl)-1-butene	75–80 (125)				
$C_{10}H_{11}Cl$	2-Chloro-1,2,3,4-tetrahydronaphthalene	100 (184, 185, 186)				
$C_{10}H_{12}$	1-Phenyl-2-methyl-1-propene	— (175)				
	1-Phenyl-1-butene	60–80 (173, 174)				
	4-Phenyl-1-butene	— (136)				
	1,2,3,4-Tetrahydronaphthalene	— (175)				
$C_{10}H_{12}O$	1-Anisyl-1-propene	60–80 (173, 174)				
$C_{10}H_{14}$	5-Phenyl-1-pentene	60–80 (173, 174)				

TABLE I—Continued

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
A. Hydrocarbons and Substituted Hydrocarbons—Continued							
C$_{10}$H$_{16}$	Camphene	— (187)		— (188)	— (189)		
	(+)-Δ^4-Carene	70 (31)		69 (31, 188)	— (31)		
	(+)-Δ^3-Carene	— (190)					
	2,4-Dimethyl-4-vinyl-1-cyclohexene	40–60 (6, 32, 101, 191, 192)		63 (32)			
	Limonene				— (193)		
	Myrcene			25 (194)			
	Norbornylene				— (195)		
	Pinene	— (6, 187, 191, 196, 197)		89 (31, 198)			— (142)
	Sabinene	— (199)					
	α-Terpinene	40 (200)					
	γ-Terpinene						
C$_{10}$H$_{18}$	1-Butyl-1-cyclohexene	— (132)					
	1,9-Decadiene	— (121)					
	2,6-Dimethyl-2,6-octadiene	— (121)					
	3-Menthene	83–91 (201)		59–80 (201)	— (140)		
	4-Methyl-2-n-propyl-1-cyclohexene	— (132)					
C$_{10}$H$_{20}$	Caprylene	— (6, 191)					
	1-Decene	100 (181)		56 (2)		45–75 (2)	
	Decene	— (6)		50 (34)			
C$_{11}$H$_{10}$	1-Phenyl-3-penten-1-yne						
C$_{11}$H$_{10}$O	1-Anisyl-1-butene	— (175)					

Formula	Compound				
$C_{11}H_{12}$	1-Phenyl-1-cyclopentene	— (10, 70, 202)			40–75 (2, 212)
$C_{11}H_{13}O_2$	3-Phenyl-1-cyclopentene	90 (203a)			
	1-(3,4-Methylenedioxyphenyl)-2-methyl-1-propene	60–80 (203, 204)			
$C_{11}H_{14}$	1-(p-Tolyl)-2-methyl-1-propene	60–80 (176, 203)			
	2-Methyl-3-phenyl-2-butene	— (205)			
	1-Phenyl-1-pentene	— (175)			
	1-Phenyl-2-methyl-1-butene	70–90 (184)			
	1-Phenyl-3-methyl-1-butene	— (175)			
	1-Anisyl-2-methyl-1-propene	— (185, 186, 206)			
$C_{11}H_{14}O$	1-(m-Methoxyphenyl)-2-methyl-1-propene	70–80 (207)			
	1-(o-Methoxyphenyl)-2-methyl-1-propene	70–80 (207)			
	2-Methylenedecahydronaphthalene	— (132)	62 (34)		
$C_{12}H_{18}$	1-Hendecene	100 (181)			
$C_{12}H_{12}$	1-Phenyl-3-hexen-1-yne	— (164)			
$C_{12}H_{16}O_4$	3,4-Diacetoxystyrene	100 (10, 70, 208, 209)			
$C_{12}H_{14}$	1-Phenyl-1-cyclohexene	— (202)			
$C_{12}H_{14}O$	1-Aminyl-1-cyclopentene	— (203a)			
	3-Aninyl-1-cyclopentene	70–90 (184)			
$C_{12}H_{16}$	1-Phenyl-2-ethyl-1-butene	70–90 (184)			
	1-Phenyl-2-methyl-1-pentene	60–80 (173, 174)			
	6-Phenyl-1-hexene	— (210)			
$C_{12}H_{16}O$	1-Anisyl-2-methyl-1-butene	— (175)			
	1-Aninyl-1-pentene	— (210)			
	3-Anisyl-2-isopentene	— (190)			
$C_{12}H_{20}$	1,2,5-Trimethyl-5-isopropenyl-1-cyclohexene	100 (181, 211)		52 (2)	
$C_{13}H_{24}$	1-Dodecene				
$C_{13}H_{14}$	Isodolorene	— (214)		(213)	
$C_{13}H_{14}O$	3-Ethoxy-4-propyl-3-heptene			40 (58)	
$C_{13}H_{14}$	1-Phenyl-3-methyl-3-hexen-1-yne	— (209)			
$C_{13}H_{18}$	1-Phenyl-4-methyl-1-cyclohexene	— (132)			
$C_{13}H_{18}$	1-Benzyl-1-cyclohexene				

TABLE I—*Continued*

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
A. Hydrocarbons and Substituted Hydrocarbons—Continued							
C₁₃H₁₈O	1-Anisyl-2-ethyl-1-butene	— (206)					
C₁₃H₂₆	1-Tridecene	100 (181)					
C₁₃H₁₀Cl₂	*trans*-1,4'-Dichlorostilbene	50 (215)					
C₁₄H₁₂	Allostilbene	— (217)		— (137)	— (210)		
	Isostilbene	60–100 (22, 185, 216, 217)		83–100 (137, 201)	— (210)		
	Stilbene					70–80 (220)	13 (218)
	1,1-Diphenylethylene						
C₁₄H₁₈	1-Phenyl-2-cyclohexylethylene		— (219)				
	1-(2,3-Dimethoxyphenyl)-1-cyclohexene						
C₁₄H₂₀O	4-Anisyl-3-heptene	— (210)					
C₁₄H₂₄	1,1-Dicyclohexylethylene	76 (221)					
C₁₄H₂₈	1-Tetradecene	— (203, 201)		42 (2, 222)		69–95 (2, 223)	
C₁₅H₁₂O₂	1-Phenyl-2-(3,4-methylenedioxy-phenyl)ethylene				100 (138)		
C₁₅H₁₄	1,1-Diphenyl-1-propene	— (100, 224, 225)					
	1,2-Diphenyl-1-propene	— (226)					
	1,3-Diphenyl-1-propene	— (175)					
	Diphenylpropene	— (170, 203, 227)					
C₁₅H₁₄O	1-Phenyl-2-(p-tolyl)ethylene	— (185, 228)					
	1-Phenyl-2-anisylethylene	— (229)					
	1-Phenyl-1-(m-methoxyphenyl)ethylene	— (229)					
	1-Phenyl-1-(o-methoxyphenyl)ethylene	— (229)					

TABLE I—Continued
ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
A. Hydrocarbons and Substituted Hydrocarbons—Continued							
$C_{24}H_{24}$	1-(2-Biphenylyl)-1-phenyl-2-ethyl-1-butene	75 (242)					
$C_{24}H_{32}$	1,1-Diphenyldodecene	— (243)					
$C_{26}H_{20}$	Tetraphenylethylene	100 (244)					
$C_{30}H_{48}$	α-Amyrilene	— (245)					
	β-Amyrilene	— (245, 246)					
	Euphatrione	— (247)					
$C_{30}H_{50}$	Unnamed hydrocarbon	— (248)					
	Dihydro-β-amyrilene	— (246)					
	Squalene	— (22)	70 (249)				
	2-Lupene		— (250)				
$C_{40}H_{56}$	α-Carotene		Good (251)				
	β-Carotene	10–15 (252)					
	Carotene (mixture of isomers)	65 (253)					
$C_{42}H_{32}$	1,2-Bis(benzyl-9-fluorenyl)ethylene	— (254, 255)					
$(C_5H_8)_n$	Rubber			— (256)	— (256, 257)		
B. Steroids (alphabetical order)							
	3β-Acetoxyallopregnan-20-one enol acetate	— (258)					

TABLE I—Continued

Ethylenic Compounds Oxidized with Organic Peracids

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid

B. *Steroids (alphabetical order)—Continued*

	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
	3-trans-Dehydroandrosterone	— (293)			— (293)		
	trans-Dehydroandrosterone acetate	50 (294)	25–60 (294, 295)				
	trans-Dehydroandrosterone benzoate		80 (294)		— (293)		
	3-trans-Dehydroandrosterone tetraacetylglucoside	— (288)					
	Dehydroergosteryl acetate-maleic anhydride adduct	Fair (296)					
	Dehydroisoandrosterone	40 (297)			25–30 (298)		
	Dehydroisoandrosterone acetate		40 (299)				
	3,6-Diacetoxy-5-methyl-10-norandrost-8(9)-en-17-one	20 (300)		30 (300)			
	3,6-Diacetoxy-5-methylnorcholestane	25 (301)	70 (259, 301)				
	3β,21-Diacetoxy-20-oxo-5-allo-14,16-pregnadione						
	Dibromodehydroergosteryl acetate-maleic anhydride adduct	80 (302)					
	3,7-Dihydroxycholenic acid	70 (303)					
	Dihydroergosteryl acetate	— (305)					— (304)
	3α,12α-Dihydroxy-14-cholenic acid						
	3,9-Epoxy-11-cholenic acid	60 (306)					— (304)
	α-Ergostenyl acetate						20 (304)
	Ergosterol			— (288)			
	Ergosterol-maleic anhydride adduct						

Compound	Yield (Reference)
Ergosteryl acetate-maleic anhydride adduct	— (302)
9-Etiocholenol-3α-one-17	— (308)
11-Etiocholen-3α-ol-17-one acetate	>60 (309)
3α-Hydroxy-9,11-cholenic acid	25 (306)
3α-Hydroxy-11-cholenic acid	80 (310)
3α-Hydroxypregnan-20-one enol acetate	— (258)
Δ²-22-Isoallospirostene	71 (315)
Δ⁹⁽¹¹⁾,22-Isoallospirosten-3β-ol-3-acetate	50 (311)
Isodihydroxycholenic acid	— (312)
3-Ketoandrosta-4,16-diene	70 (313)
α-Methoxy-16-i-pregnen-20-one	— (314)
Methyl 3β-acetoxy-14,16-alloetiocholadienate	— (316)
Methyl 3β-acetoxyallo-14-etiocholenate	80 (269)
Methyl 3β-acetoxy-5,11,16-cholntrienate	— (317)
Methyl 3α-acetoxy-9,11-cholenate	60–70 (284, 288, 318)
Methyl 3α-acetoxy-11-cholenate	50 (318, 319)
Methyl 3β-acetoxy-11-cholenate	40 (319)
Methyl 3β-acetoxy-14,16-etioallocholadienate	— (259, 307)
Methyl 3β-acetoxy-11,16-etiocholadienate	100 (320)
Methyl 3α-acetoxy-9(11)-etiocholanate	— (321)
Methyl 3β-acetoxy-3β-etioallocholenate	— (259)
Methyl 3α-acetoxy-12α-hydroxy-7-cholenate	30 (322)
Methyl 3β-acetoxy-14,17-isoalletiocholenate	80 (269)
Methyl 0-cholenate	— (323)
Methyl 11-cholenate	— (318, 324)
Methyl 7,14-3α,12β-diacetoxycholn-dienate	— (274)

TABLE I—Continued

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Ethylenic Compound		Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
	B. Steroids (alphabetical order)—Continued						
	Methyl 3α,12α-diacetoxy-11-cholenate	— (250)					
	Methyl 3α,12β-diacetoxy-11-cholenate	50 (274)					
	Methyl diacetylapocholate	— (312)					
	Methyl 3α,12β-diacetylapocholate	— (274)					
	Methyl 3,7-dihydroxycholenate	— (271)					
	Methyl 3α-hydroxy-11-cholenate	45 (319)					
	Methyl 3β-hydroxy-11-cholenate	55 (319)					
	Methyl 3α-hydroxy-12-methoxy-9,11-cholenate	95 (325)					
	Methyl 3-keto-1,11-choladienate	— (326)					
	Methyl 3-keto-11-cholenate	70 (326)					
	Methyl 9(11)-lithocholenate	— (325)					
	Methyl 12-methoxy-9,11-cholenate		>40 (327)				
	5-Methylnorcholestane-3,6-dione			55 (300)			
	3-Methyl-A-nor-3(5)-cholestene		— (328)				
	5,16-Pregnadien-3β-ol-20-one acetate	56 (314, 329)					
	14,17-Pregnadien-3-one		— (330)				
	5-Pregnen-20-one-3β-21-diol 21-mono-acetate	70 (297)			25 (298)		
	Pregnenolol acetate		65 (263, 331)				
	17-Vinyl-3,17-isoandrostanediol						— (272)

TABLE I—Continued

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Formula	Ethylenic Compound Name	Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
		Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
	C. Acids—Continued						
$C_{18}H_{34}O_2$ (*Cont'd*)	*cis*-10-Octadecenoic					69 (350)	
	trans-10-Octadecenoic					88 (350)	
	cis-11-Octadecenoic		— (366a)			73–94 (350, 366a, 367)	
	trans-11-Octadecenoic					80–94 (349, 350, 367a)	
	cis-12-Octadecenoic					68 (350)	
	trans-12-Octadecenoic					60 (350)	
	Vaccenic						
$C_{18}H_{34}O_3$	*cis*-12-Hydroxy-9-octadecenoic (ricinoleic)				20 (368), — (369)		
	trans-12-Hydroxy-9-octadecenoic (ricinelaidic)				— (369)		
$C_{20}H_{36}O_4$	α-9-Octadecene-1,18-dicarboxylic			— (370)	74 (340)	57 (373)	
$C_{20}H_{38}O_2$	*n*-11-Eicosenoic				40 (371, 372)		
$C_{22}H_{32}O_3$	Anacardic				— (344)		
$C_{22}H_{38}O_6$	9,10-Diacetoxy-12-octadecenoic				— (338)		
$C_{22}H_{40}O_4$	Hendecenoic dimers				— (357)		
$C_{22}H_{42}O_2$	Brassidic	55 (357)			58 (338, 357)		— (171)
	Erucic	70 (171, 357)					— (171)
$C_{30}H_{48}O_3$	α-Elemolic		— (374)				
$C_{11}H_{20}O_2$–$C_{22}H_{42}O_2$	Mixed unsaturated fatty acids from human hair fat					— (375)	

TABLE I—Continued

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

Formula	Name	Yield of Oxirane, % (Reference)			Yield of α-Glycol, % (Reference)		
		Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
E. Esters							
C$_4$H$_6$O$_2$	Vinyl acetate						
C$_6$H$_8$O$_2$	Methyl 2,4-hexadienoate (sorbate)	— (398, 399)				— (370)	
C$_6$H$_{10}$O$_3$	Ethyl acetoacetate	— (100)					
C$_7$H$_{12}$O$_2$	1-Acetoxy-1-cyclohexene	— (125)					
C$_8$H$_{14}$O$_3$	1-Acetoxy-3-methyl-1-cyclohexene	— (101)					
	2-Acetoxy-2-methyl-1-cyclohexene	— (125, 180)					
	Methyl diallylacetate	— (121)					
C$_9$H$_{16}$O$_4$	Diethyl allylmalonate		>32 (102)	32 (102)		50 (55)	
C$_{10}$H$_{18}$O$_2$	Methyl 2-nonenone						
C$_{11}$H$_{12}$O$_2$	Cinnamyl acetate	70 (377)					
C$_{11}$H$_{16}$O$_2$	Methyl α-allocyclogeranate		65 (103)				
C$_{11}$H$_{18}$O$_4$	Diethyl (1-methyl-2-propenyl)malonato		51 (102)				
C$_{13}$H$_{16}$O$_4$	Ethyl α-cyclogeranato		60 (103)				
C$_{12}$H$_{20}$O$_2$	Methyl 1,1,3-trimethyl-3-cyclohexene-2-acetate		60 (335)				
C$_{13}$H$_{22}$O$_3$	Ethyl 5-cyclopentyl-5-hydroxy-2-pentenone			40 (1, 23)		30 (401)	
C$_{13}$H$_{24}$O$_2$	Methyl 10-hendecenoate (undecylenate)	— (387)			— (405)		
C$_{13}$H$_{20}$O$_4$	Diethyl diallylmalonate	— (121)					
C$_{13}$H$_{24}$O$_2$	Ethyl 10-hendecenoate (undecylenate)	— (387)			— (405)		
C$_{14}$H$_{26}$O$_3$	Ethyl 5-hydroxy-2-hendecenoate						
C$_{14}$H$_{22}$O$_4$	Dimethyl traumatate					20 (401)	
C$_{14}$H$_{26}$O$_2$	Propyl 10-hendecenoate (undecylenate)				— (405)	— (55)	
C$_{14}$H$_{26}$O$_3$	2-Methoxyethyl 10-hendecenoate (undecylenate)				— (405)		

	Compound					
C₁₇H₃₂O₂	Methyl palmitoleate	25–10 (28, 29, 345, 406)		— (28, 29, 30)	— (49)	
C₁₉H₃₄O₂	Methyl 9,12-octadecadienoate (linolenate)	20 (29, 310)		45 (1, 23, 355)	50 (49, 72, 107) <20 (315)	96 (37,* 36)
	Methyl 9,11-octadecadienoate	42–67 (3, 20)		— (72)	— (49, 107)	
C₁₉H₃₆O₂	Methyl cis-9-octadecenoate (oleate)	— (171)			— (409)	
	Methyl trans-9-octadecenoate (elaidate)	80 (408)				
	Methyl cis-6-octadecenoate (petroselinate)					
	Methyl trans-6-octadecenoate (petroselaidate)	— (408)		— (1, 23)		30 (56, 109?) 100 (1, 169)
C₁₉H₃₆O₃	Methyl hydroxyoleates	80 (29)				
	Methyl cis-12-hydroxy-9-octadecenoate (ricinoleate)	85–95 (28, 20)				
	Methyl trans-12-hydroxy-9-octadecenoate (ricinelaidate)				— (311)	
C₂₀H₃₄O₂	Ethyl 9,11,13-octadecatrienoate (eleostearate)	(343)				
	Ethyl 9,12,15-octadecatrienoate (linolenate)	— (171, 240, 342, 343)		40 (410)	— (29, 51, 361, 362)	
C₂₀H₃₈O₂	Ethyl cis-9-octadecenoate (oleate)	— (240)			— (29)	
	Ethyl trans-9-octadecenoate					
	Oleyl acetate		— (412)	— (355)		
C₂₁H₃₂O₂	Methyl (+)-pimarate	— (411)				
C₂₁H₃₄O₂	Methyl (+)-dihydropimarate	— (411) — (357)				
C₂₃H₄₄O₂	Methyl brassidate	— (357)			Good (357)	
	Methyl erucate	75 (357)			— (357)	
C₂₆H₅₀O₂	Octyl oleate		— (374)			
C₃₁H₅₀O₃	Methyl α-elemolate					
C₃₂H₅₂O₂	β-Amyrin acetate	— (247)		— (413)		
	Euphadienyl acetate	— (414)				
	Euphorbadienyl acetate	— (395)				
	Euphol acetate	— (415)				
	Germanicol acetate		— (418)			
	Lanosteryl acetate	— (416, 417)		— (118a)		
	Taraxerol acetate					
C₃₂H₅₄O₂	Artenyl acetate	— (247)				— (37)
	Euphenyl acetate					

* Oxirane formed.

TABLE I—*Continued*

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

| Ethylenic Compound | | Yield of Oxirane, % (Reference) | | | Yield of α-Glycol, % (Reference) | | |
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
		E. Esters—Continued					
$C_{32}H_{52}O_2$ (Cont'd)	Euphorbenyl acetate	— (247)					
	Isodihydroeuphol acetate	70 (420)					
	Tirucallenyl acetate	— (247)					
	Methyl acetyleburicoate	— (421)					
$C_{33}H_{52}O_4$	Oleyl oleate	— (418a)					
$C_{36}H_{68}O_2$	Artenyl benzoate						
$C_{37}H_{56}O_2$	Escingenin tetraacetate		— (422)				
$C_{38}H_{56}O_9$	Propylene glycol diolate			— (355)			
$C_{39}H_{72}O_4$	Isoescsingenin pentaacetate		— (423)				
$C_{40}H_{68}O_{10}$	Diethylenerglycol diolate		— (424)	— (355)			
$C_{40}H_{74}O_6$	Cryptoxanthin diacetate		6 (425)				
$C_{44}H_{60}O_3$	Xanthophyll diacetate		— (425)				
$C_{44}H_{60}O_4$	Zeaxanthin diacetate		— (426)				
	Capsanthin diacetate						
$C_{44}H_{62}O_5$	Triolein			86 (1, 427)		— (37)	
$C_{57}H_{104}O_6$	Butyl Carbitol esters of unsaturated fatty acids			— (355)			
	Castor oil			73 (1, 427)	36 (52, 361, 362, 369, 428)		
	Cocoa butter				— (50)		
	Coconut oil				— (428)		
	Corn oil			70–80 (1, 427, 429)			

Compound					
Cottonseed oil			71 (1, 427)		
Lard oil			74 (1, 427)		
Linseed oil			66 (1, 427)		
Menhaden oil			57 (1, 427)		
Methyl esters of soybean oil acids			— (355)		
Methyl esters of unsaturated acids			— (355)		
Neatsfoot oil			77 (1, 427)		
Olive oil			81 (1, 427)		
Peanut oil			75 (1, 427)		
Perilla oil			64 (1, 427)		
Rapeseed oil			71 (1, 427)		
Rice oil		— (428)			
Sardine oil	— (430)	— (431–436)	67–75 (1, 427, 429)		
Soybean oil	— (37,* 434)	— (419) / — (358, 437)			
Tall oil		— (50)			
Tallow					
Tobaccoseed oil			73 (1, 427)		

F. Aldehydes and Ketones (including carbohydrate derivatives)

Formula	Compound				
$C_6H_{10}O_3$	Rhamnal				
$C_6H_{10}O_4$	Galactal				
	Glucal	— (438, 439)			75 (438, 439)
$C_7H_{12}O_4$	3-Methylglucal	— (8)			— (440)
$C_8H_{14}O$	Methylheptenone	— (9)			— (438, 441)
$C_{10}H_{10}O$	Benzylideneacetone	— (6, 9)			30 (442)
$C_{10}H_{16}O$	Citral	59 (443)			
	Pulegone	— (6, 8)			
$C_{10}H_{18}O$	Citronellal				
$C_{12}H_{16}O_7$	Triacetylgalactal				33 (440)
	Triacetylglucal				30 (441, 442)
$C_{12}H_{20}O_9$	Lactal	— (446)			— (444)
	Cellobial	96.5 (445)	60–70 (446)		
$C_{13}H_{20}O$	α-Ionone	86 (445)	50 (447)		90 (439)
	β-Ionone				
$C_{13}H_{22}O$	α-Dihydroionone				

* Oxirane formed.

TABLE I—*Continued*

ETHYLENIC COMPOUNDS OXIDIZED WITH ORGANIC PERACIDS

| Ethylenic Compound | | Yield of Oxirane, % (Reference) | | | Yield of α-Glycol, % (Reference) | | |
Formula	Name	Perbenzoic Acid	Monoperphthalic Acid	Peracetic Acid	Peracetic Acid	Performic Acid	Perbenzoic Acid
F. Aldehydes and Ketones (including carbohydrate derivatives)—Continued							
$C_{13}H_{22}O$	11-Keto-1-tridecene	— (387)					
$C_{14}H_{18}O_9$	Tetraacetyl-1-glucosene		60 (445)				
$C_{14}H_{22}O$	Methyl α-ionone	45–55 (387)					
$C_{14}H_{26}O$	11-Keto-1-tetradecene		85 (449)				
$C_{15}H_{28}O_2$	α-Dihydroionone ethylene ketal	— (387)					
$C_{17}H_{24}O$	11-Keto-11-phenyl-1-hendecene	— (410)					
$C_{30}H_{48}O$	Lanostenone	— (247)					
$C_{30}H_{50}O$	Euphenone						30 (448)
G. Ethers							
C_4H_4O	Furan	25 (451)					
C_4H_8O	Ethyl vinyl ether	58 (452)					
C_6H_8O	5,6-Dihydro-1,2-pyran	— (121)					— (450)
$C_6H_{10}O$	Diallyl ether	45 (170)				71 (453)	
$C_6H_{10}O_2$	2-Propenyldioxolane	35 (454)				25–33 (455)	
$C_9H_{10}O$	Phenyl allyl ether				100 (138)		
$C_9H_{16}O_3$	α,α'-Diallylglycerol				— (138) 55–100 (32, 138)		
$C_{10}H_{10}O_2$	Isosafrole	— (203)					
	Safrole			62 (24)	100 (138)		
$C_{10}H_{12}O$	Anethole	85 (377, 457)					
	Methyl cinnamyl ether						
$C_{10}H_{12}O_2$	Eugenol				100 (138)		— (456)

H. Miscellaneous

Formula	Compound	Yield % (Reference)
C11H14O	Isoeugenol	— (32)
	Ethyl cinnamyl ether	— (457)
C12H14O	Allyl cinnamyl ether	50 (454)
C12H14O2	Hydroquinone diallyl ether	25 (454)
C14H22O	Dispiro[dicyclohexane-2,5-dihydrofuran]	60 (458)
C22H36O	Cardanol methyl ether	95 (159)
C4H6O2S	Butadiene sulfone	8 (462)
C5H8O2S	β-Isoprene sulfone	30 (463)
C6H10O2S	Dimethylbutadiene sulfone	— (464)
C7H13NO	2-Ethyl-2-pentenamide	— (461)
	2-Ethyl-2-hexenamide	69 (461)
C8H15NO	2-Propyl-2-pentenamide	85 (461)
C9H10O3	Furfural diacetate	60 (463)
C10H12O2S	Benzyl propenyl sulfone	— (460)
C11H10N4O	Furfuralphenylhydrazone	60 (460)
C11H12N2S	Thiopyrine	— (460)
C13H12N2	Benzaldehydephenylhydrazone	— (460)
C15H20O4	ψ-Santonin	— (339)
C18H35NO	Oleamide	65 (465, 466)
C19H37NO	N-Methyloleamide	38 (465, 466)
C20H37NO2	N-Acetyloleamide	29 (465, 466)
	n-11-Eicosenamide	59 (465, 466)
C20H39NO2	N-(2-Hydroxyethyl)oleamide	45 (465, 466)
	N-Phenyloleamide	53 (465, 466)
C24H39NO	N-(n-Hexyloleamide)	— (370)
C24H47NO	α-Phellandrene-β-naphthol adduct (p-nitrobenzoate)	90 (467)
C22H27NO4	N-(α-Naphthyl)oleamide	— (466)
C28H41NO	N-(n-Decyl)oleamide	89 (465, 466)
C28H55NO2	N-(n-Dodecyl)oleamide	45 (465, 466)
C30H59NO2	N-Amylamides of unsaturated fatty acids	— (355)
	N,N-Dibutylamides of unsaturated fatty acids	— (355)

ADDENDUM TO TABLE I

The compounds appearing in this addendum are listed alphabetically in sections which correspond to those in Table I.

Compound	Peracid	Product	Yield	Reference
A. Hydrocarbons and Substituted Hydrocarbons				
3-Acetoxy-1-cyclohexene	Peracetic, performic	Triol	20–25	468
α-Amrylene	Peracetic	Oxirane	—	469
1-(2-Biphenyl)-3,4-dihydronaphthalene	Monoperphthalic	Oxirane	—	470
α-Cyclohexylideneethylbenzene	Performic	Glycol	42	471
α-Cyclohexylstyrene	Performic	Glycol	42	471
3-Methoxy-1-cyclohexene	Peracetic	Glycol	30	468
1-Phenyl-1-(2-biphenylyl)ethylene	Perbenzoic	Aldehyde (via the oxirane)	—	470
B. Steroids				
3β-Acetoxy-7,8-epoxy-9(11),22-ergostadiene dibromide	Perbenzoic	Glycol	—	472
3β-Acetoxy-7,9(11),20-ergostatriene	Perbenzoic	Oxirane	—	472
3β-Acetoxy-7,9,22-ergostatriene	Monoperphthalic	Oxirane	—	473
16,20(22)-Allofurostadiene-3β,26-diol diacetate	Monoperphthalic	Oxirane	—	474
Allopregnane-11,20-dienol acetate	Perbenzoic	Glycol	—	475
8(14)-Androsten-3β,17β-diol diacetate	Monoperphthalic	Oxirane	10–35	476
9-Androsten-3α-ol-17-one	Perbenzoic	Oxirane	—	477
3β-Benzoxy-7,9(11)-cholestadiene	Monoperphthalic	Oxirane	70	478
3β-Benzoxy-7-cholestene	Monoperphthalic	Oxirane	50	478
2-Cholesten-6-one	Perbenzoic	Oxirane	—	479
3β,17β-Diacetoxy-7,9(11)-androstadiene	Monoperphthalic	Oxirane	40	478
22,23-Dibromo-3β-acetoxy-7,9(11)-ergostadiene	Peracetic	Oxirane	—	472
7,9(11),22-Ergostatrien-3β-ol acetate	Perbenzoic	Oxirane	—	480
9-Etiocholen-3α-ol-17-one	Perbenzoic	Oxirane	—	477
Methyl 3α-acetoxy-7,9-choladienate	Monoperphthalic	Oxirane	—	473
Methyl 3α-hydroxy-9(11)-cholenate	Perbenzoic	Oxirane	—	481
5β-Methyl-3β-methoxy-19-norcoprost-9(10)-en-6-one	Peracetic	Oxirane	—	482
5β-Methyl-19-norcoprost-9(10)-en-3β,6β-diol diacetate	Peracetic	Oxirane	—	482
9(11),17(20)-Pregnadiene-3α,11,20-triol triacetate	Perbenzoic	Oxirane	—	483
9(11)-Tigogenin acetate	Perbenzoic	Oxirane	—	481
C. Acids				
cis-9-Hendecenoic	Performic	Glycol	30	484
trans-9-Hendecenoic	Performic	Glycol	55	484

ADDENDUM TO TABLE I—*Continued*

Compound	Peracid	Product	Yield	Reference
E. Esters				
α-Amyrin acetate	Peracetic	Oxirane	20	469
α-Amyrin benzoate	Peracetic	Oxirane	50	469
cis-2-Buten-1,4-diol diacetate	Peracetic	Tetraacetate	57	485
trans-2-Buten-1,4-diol diacetate	Peracetic, performic	Tetraacetate, formates	51–79	485
			—	486
Methyl acetyleburicoate	Perbenzoic	Oxirane	80	487
Methyl morolate acetate	Perbenzoic, peracetic	Oxirane	—	487
Methyl morolate benzoate	Peracetic	Oxirane	—	487
Moradiol diacetate	Peracetic	Oxirane	—	488
α-Noramyrenonyl acetate	Perbenzoic	Oxirane	—	489
Peach oil	Peracetic	Not isolated	—	490
Zeorinin acetate	Peracetic	Oxirane	—	490
Zeorinin benzoate	Peracetic	Oxirane		
G. Ethers				
Butyl p-(2-methylalloxy)benzoate	Peracetic	Glycol	50	491
m-Carbobutoxyphenyl 2-methallyl ether	Peracetic	Glycol	—	491
4-Chloro-3-methylphenyl 2-methallyl ether	Peracetic	Glycol	50	491
p-Chlorophenyl 2-methallyl ether	Peracetic	Glycol + oxirane	—	491
3,5-Dimethylphenyl 2-methallyl ether	Peracetic, performic	Glycol	6–50	491
2-Methallyl m-nitrophenyl ether	Peracetic	Glycol	33	491
2-Methallyl phenyl ether	Peracetic	Glycol + oxirane	42 + 25	491
2-Methallyl m-tolyl ether	Peracetic, performic	Glycol	6–25	491
2-Methallyl o-tolyl ether	Peracetic	Glycol + oxirane	20	491
2-Methallyl p-tolyl ether	Peracetic	Glycol + oxirane	—	492
5,6-Dihydro-2-pyran	Performic	Glycol	60	492
2,5-Dihydro-2,2,5,5-tetramethylfuran	Performic	Oxirane	25	
H. Miscellaneous				
2-Methallyl chloride	Peracetic	Glycol	—	491

REFERENCES FOR TABLE I

[120] Tomisek and Mahler, *J. Am. Chem. Soc.*, **73**, 4685 (1951).

[121] Everett and Kon, *J. Chem. Soc.*, **1950**, 3131.

[122] Himel and Edmonds, U. S. pat. 2,555,927 [*C. A.*, **46**, 524 (1952)].

[123] Owen, *J. Chem. Soc.*, **1949**, 241.

[124] British Drug Houses, Ltd., Bradley, Forrest, and Stephenson, Brit. pat. 613,735 [*C. A.*, **42**, 473 (1949)].

[125] Mousseron and Jacquier, *Bull. soc. chim. France*, **1950**, 698.

[126] Mousseron, Winternitz, and Jacquier, *Compt. rend.*, **223**, 1014 (1946.)

[127] Wieland, Bergel, Schwarz, Schepp, and Fukelman, *Ann.*, **446**, 13 (1925).

[128] G. W. Reindel, thesis, University of Erlangen, 1931 [*C. A.*, **27**, 1637 (1933)].

[129] Böeseken, *Rec. trav. chim.*, **54**, 657 (1935).

[130] Mousseron, Winternitz, Jullien, and Jacquier, *Bull. soc. chim. France*, **1948**, 79.

[131] Bedos and Ruyer, *Compt. rend.*, **195**, 802 (1932).

[132] Mousseron, Richaud, Granger, Winternitz, Combes, Canals, Souche, Cabanes, and Froger, *Bull. soc. chim. France*, **1946**, 629.

[133] Mousseron, Winternitz, and Jacquier, *Bull. soc. chim. France*, **1948**, 260.

[134] Mousseron, Winternitz, and Jacquier, *Bull. soc. chim. France*, **1947**, 81.

[135] Böeseken, *Rec. trav. chim.*, **45**, 838 (1926).

[136] Kötz and Hoffman, *J. prakt. Chem.*, [2] **110**, 101 (1925).

[137] Böeseken and Schneider, *J. prakt. Chem.*, [2] **131**, 285 (1931).

[138] Böeseken and Elsen, *Rec. trav. chim.*, **48**, 363 (1929).

[139] Rigby, *J. Chem. Soc.*, **1950**, 1907.

[140] Schering-Kahlbaum A.G., Ger. pat. 574,838 [*C. A.*, **27**, 4540 (1933)].

[141] Adkins and Roebuck, *J. Am. Chem. Soc.*, **70**, 4041 (1948).

[142] Treibs and Schulz, *Chem. Ber.*, **80**, 214 (1947).

[143] Wiggins and Wood, *J. Chem. Soc.*, **1950**, 1566.

[144] Lutz, Bearse, Leonard, and Croxton, *J. Am. Chem. Soc.*, **70**, 4139 (1948).

[145] Paul and Tchelitcheff, *Bull. soc. chim. France*, **1948**, 896.

[146] Paul and Tchelitcheff, *Compt. rend.*, **225**, 1334 (1947).

[147] Hackmann, Dutch pat. 63,605 [*C. A.*, **43**, 7503 (1949)].

[148] Cahnmann and Daniels, U. S. pat. 2,501,026 [*C. A.*, **44**, 5902 (1950)].

[149] Nazarov and Akhren, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk.*, **1950**, 621 [*C. A.*, **45**, 8516 (1951)].

[150] Mousseron, Jullien, and Winternitz, *Bull. soc. chim. France*, **1948**, 878.

[151] Mousseron, Winternitz, and Jullien, *Bull. soc. chim. France*, **1947**, 80.

[152] Böeseken and Derx, *Rec. trav. chim.*, **40**, 529 (1921).

[153] Nametkin and Jarzeff, *Ber.*, **56**, 1803 (1923).

[154] Nametkin and Brussoff, *Ber.*, **56**, 1807 (1923).

[155] Mousseron, Manon, and Combes, *Bull. soc. chim. France*, **1949**, 396.

[156] Tiffeneau, Weill, and Tchoubar, *Compt. rend.*, **205**, 54 (1937).

[157] Prileschajew, *Ber.*, **59**, 194 (1926).

[158] Levy and Pernot, *Bull. soc. chim. France*, [4] **49**, 1838 (1931).

[159] Favorskii, Chichonkin, and Ivanov, *Compt. rend.*, **199**, 1229 (1934).

[160] Reppe, Schichting, Klager, and Toepel, *Ann.*, **560**, 1 (1948).

[160a] Friess and Boekelheide, *J. Am. Chem. Soc.*, **71**, 4144 (1949).

[161] Cope and Tiffany, *J. Am. Chem. Soc.*, **73**, 4158 (1951).

[162] Benoit, *Bull. soc. chim. France*, [5] **6**, 708 (1939).

[163] Böeseken and Derx, *Rec. trav. chim.*, **40**, 519 (1921).

[164] Kaelin, *Helv. Chim. Acta*, **30**, 2133 (1947).

[165] Abbott, U. S. pat. 2,553,996 [*C. A.*, **45**, 7820 (1951)].

[165a] Craig, U. S. pat. 2,571,208 [*C. A.*, **46**, 3563 (1952)].

[166] Nametkin and Delektorski, *Ber.*, **57**, 583 (1924).

[167] Mousseron, Winternitz, and Combes, *Bull. soc. chim. France*, **1947**, 79.

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[168] I. G. Farbenindustrie A.G., Fr. pat. 816,055 [*C. A.*, **32**, 1277 (1938)].
[169] Swern, Scanlan, and Findley, U. S. pat. 2,492,201 [*C. A.*, **44**, 3521 (1950)].
[170] Fourneau and Chantalou, *Bull. soc. chim. France*, [5] **12**, 845 (1945).
[171] Bauer and Bähr, *J. prakt. Chem.*, [2] **122**, 201 (1929).
[172] Quelet, *Bull. soc. chim. France*, [4] **45**, 75 (1929).
[173] Levy and Sfiras, *Bull. soc. chim. France*, [4] **49**, 1823 (1931).
[174] Levy and Sfiras, *Compt. rend.*, **184**, 1335 (1927).
[175] Levy and Dvoleitzka-Gombinska, *Bull. soc. chim. France*, [4] **49**, 1765 (1931).
[176] Tiffeneau and Levy, *Compt. rend.*, **184**, 1465 (1927).
[177] Danilov and Venus-Danilova, *Ber.*, **60**, 1050 (1927).
[178] Criegee and Zogel, *Chem. Ber.*, **84**, 215 (1951).
[179] Mousseron and Granger, *Compt. rend.*, **218**, 358 (1944).
[180] Mousseron, Winternitz, Granger, Claret, Trinquier, and Combes, *Bull. soc. chim. France*, **1947**, 598.
[181] Rothstein, *Bull. soc. chim. France*, [5] **2**, 1936 (1935).
[182] Tchoubar, *Compt. rend.*, **214**, 117 (1942).
[183] Muskat and Herrman, *J. Am. Chem. Soc.*, **54**, 2001 (1932).
[184] Levy and Tabart, *Bull. soc. chim. France*, [4] **39**, 763 (1926).
[185] Tiffeneau and Levy, *Bull. soc. chim. France*, [4] **49**, 1776 (1931).
[186] Tiffeneau, Orekhoff, and Levy, *Compt. rend.*, **179**, 977 (1924).
[187] Faidutti, *Compt. rend.*, **189**, 854 (1929).
[188] Isaeva and Arbuzov, *Zhur. Obshcheĭ Khim.*, **19**, 893 (1944) [*C. A.*, **44**, 3467 (1950)].
[189] Pillay and Simonsen, *J. Chem. Soc.*, **1928**, 359.
[190] Lebedev and Merezhkovskiĭ, *J. Russ. Phys. Chem. Soc.*, **45**, 1249 (1913) [*C. A.*, **8**, 321 (1914)].
[191] Prileschajew, Ger. pat. 230,723 [*C. A.*, **5**, 2699 (1911)].
[192] Schmidt, *Chem. Ber.*, **82**, 11 (1949).
[193] Sword, *J. Chem. Soc.*, **127**, 1632 (1925).
[194] Pigulevskii and Prokudina, *Doklady Akad. Nauk S.S.S.R.*, **67**, 511 (1949) [*C. A.*, **44**, 1399 (1950)].
[195] Birch, Oldham, and Johnson, *J. Chem. Soc.*, **1947**, 818.
[196] Nametkin and Jarzeff, *J. Russ. Phys. Chem. Soc.*, **55**, 521 (1924) [*C. A.*, **19**, 2818 (1925)].
[197] Prileschajew and Vershuk, *J. Russ. Phys. Chem. Soc.*, **61**, 445 (1929) [*C. A.*, **24**, 607 (1930)].
[198] Isaeva and Arbusov, *Zhur. Obshcheĭ Khim.*, **19**, 884 (1949) [*C. A.*, **44**, 3466 (1950)].
[199] Elson, Gibson, and Simonsen, *J. Chem. Soc.*, **132**, 2732 (1929).
[200] Richter and Presting, *Ber.*, **64**, 1878 (1931).
[201] Tanaka, *Mem. Coll. Sci., Kyoto Imp. Univ.*, **A22**, 97 (1939) [*C. A.*, **34**, 403 (1940)].
[202] Mousseron and Winternitz, *Compt. rend.*, **229**, 56 (1949).
[203] Tiffeneau and Levy, *Bull. soc. chim. France*, [4] **49**, 1738 (1931).
[203a] Winternitz and Mousseron, *Bull. soc. chim. France*, **1949**, 713.
[204] Tiffeneau and Levy, *Compt. rend.*, **190**, 1510 (1930).
[205] Lyepin, *J. Russ. Phys. Chem. Soc.*, **44**, 1165 (1912) [*C. A.*, **7**, 982 (1913)].
[206] Tiffeneau, Levy, and Weill, *Bull. soc. chim. France*, [4] **49**, 1709 (1931).
[207] Levy and Pernot, *Bull. soc. chim. France*, [4] **49**, 1721 (1931).
[208] Levy and Sfiras, *Bull. soc. chim. France*, [4] **49**, 1830 (1931).
[209] Nametkin and Ivanoff, *Ber.*, **56**, 1805 (1923).
[210] Weill, *Bull. soc. chim. France*, [4] **49**, 1795 (1931).
[211] Baumgarten, *Ber.*, **75**, 977 (1942).
[212] Swern and Billen, U. S. pat. appl. 675,120; *Official Gaz. U. S. Pat. Office*, **648**, 948 (1951) [*C. A.*, **47**, 604 (1953)].
[213] I. G. Farbenindustrie A.G., Fr. pat. 816,055 [*C. A.*, **32**, 1277 (1938)].
[214] Badran, *Bull. soc. chim. France*, [4] **49**, 1551 (1931).
[215] Lutz and Murphey, *J. Am. Chem. Soc.*, **71**, 478 (1949).
[216] Böeseken and Elsen, *Rec. trav. chim.*, **47**, 694 (1928).

[217] Kayser, *Compt. rend.*, **196**, 1127 (1933).

[218] Newbold and Spring, *J. Chem. Soc.*, **1945**, 247.

[219] Tiffeneau and Kuriaki, *Compt. rend.*, **209**, 465 (1939).

[220] Bergmann, Pappo, and Ginsburg, *J. Chem. Soc.*, **1950**, 1369.

[221] Venus-Danilova, *J. Russ. Phys. Chem. Soc.*, **61**, 1479 (1929) [*C. A.*, **24**, 1354 (1930)].

[222] Swern and Billen, U. S. pat. 2,457,328 [*C. A.*, **43**, 3446 (1949)].

[223] Swern and Billen, U. S. pat. appl. 675,121; *Official Gaz. U. S. Pat. Office*, **649**, 603 (1951) [*C. A.*, **47**, 1184 (1953)].

[224] Levy and Lagrave, *Compt. rend.*, **180**, 1032 (1925).

[225] Weill, *Bull. soc. chim. France*, [4] **49**, 1811 (1931).

[226] Tiffeneau and Levy, *Bull. soc. chim. France*, [4] **49**, 1806 (1931).

[227] Weill and Kayser, *Bull. soc. chim. France*, [5] **3**, 841 (1936).

[228] Tiffeneau and Levy, *Compt. rend.*, **182**, 391 (1926).

[229] Levy and Pernot, *Bull. soc. chim. France*, [4] **49**, 1730 (1931).

[230] Rydon, *J. Chem. Soc.*, **1939**, 537.

[231] Treibs, *Chem. Ber.*, **80**, 56 (1947).

[232] Briggs and Taylor, *J. Chem. Soc.*, **1947**, 1338.

[233] Dev and Guha, *J. Indian Chem. Soc.*, **26**, 263 (1949) [*C. A.*, **44**, 3949 (1950)].

[234] Naves and Perrottet, *Helv. Chim. Acta*, **24**, 789 (1941).

[235] Ramart-Lucas and Salmon-Legagneur, *Bull. soc. chim. France*, [4] **45**, 718 (1929).

[236] Levy and Dvoleitzka-Gombinska, *Bull. soc. chim. France*, [4] **49**, 1765 (1931).

[237] Ramart-Lucas and Salmon-Legagneur, *Bull. soc. chim. France*, [4] **51**, 1069 (1932).

[238] Böhme Fettchem. G.m.b.H., Fr. pat. 795,391 [*C. A.*, **30**, 5238 (1936)].

[239] Grün, U. S. pat. 2,138,917 [*C. A.*, **33**, 2249 (1939)].

[240] Böeseken and Belinfante, *Rec. trav. chim.*, **45**, 914 (1926).

[241] Lane and Walters, *J. Am. Chem. Soc.*, **73**, 4234 (1951).

[242] Bradsher, Rapoport, and Anderson, *J. Am. Chem. Soc.*, **68**, 2152 (1946).

[243] Elphimoff-Felkin, *Bull. soc. chim. France*, **1950**, 494.

[244] Levy and Lagrave, *Bull. soc. chim. France*, [4] **43**, 437 (1928).

[245] Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, **15**, 482 (1932).

[246] Ruzicka, Silbermann, and Pieth, *Helv. Chim. Acta*, **15**, 1285 (1932).

[247] Barbour, Bennett, and Warren, *J. Chem. Soc.*, **1951**, 2540.

[248] Nowak, Jeger, and Ruzicka, *Helv. Chim. Acta*, **32**, 323 (1949).

[249] Jeger, Montavon, Nowak, and Ruzicka, *Helv. Chim. Acta*, **30**, 1869 (1947).

[250] Karrer and Jucker, *Helv. Chim. Acta*, **28**, 471 (1945).

[251] Karrer and Jucker, *Helv. Chim. Acta*, **28**, 427 (1945).

[252] Euler, Karrer, and Walker, *Helv. Chim. Acta*, **15**, 1507 (1932).

[253] Fuson, DeWald, and Gaertner, *J. Org. Chem.*, **16**, 21 (1951).

[254] Pummerer and Burkard, *Ber.*, **55**, 3458 (1922).

[255] Pummerer and Rebmann, *Ber.*, **61**, 1099 (1928).

[256] Kambara, Muramatsu, Maruyama, and Tokimoto, *J. Soc. Chem. Ind. Japan*, **46**, 41, 1259 (1943) [*C. A.*, **43**, 1595 (1949)].

[257] Kambara and Muramatsu, *J. Soc. Rubber Ind. Japan*, **16**, 676 (1943) [*C. A.*, **44**, 3283 (1950)].

[258] Kritchevsky and Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951).

[259] Ciba, Ltd., Brit. pat. 623,586 [*C. A.*, **44**, 3044 (1950)].

[260] Plattner, Ruzicka, Heusser, and Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

[261] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949).

[262] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, **32**, 1070 (1949).

[263] Kathol, Logemann, and Serini, *Naturwissenschaften*, **25**, 682 (1937).

[264] Seebeck and Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).

[265] Salmon and Reichstein, *Helv. Chim. Acta*, **30**, 1929 (1947).

[266] Lardon and Reichstein, *Helv. Chim. Acta*, **34**, 756 (1951).

[266a] Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937).

[267] Shoppee, *Helv. Chim. Acta*, **30**, 766 (1947).

[268] Reich and Lardon, *Helv. Chim. Acta*, **30**, 329 (1947).

[259] Plattner, Ruzicka, Heusser, and Meier, *Helv. Chim. Acta*, **29**, 2023 (1946).
[270] Wieland and Dane, *Z. physiol. Chem.*, **212**, 263 (1932).
[271] Borsche and Todd, *Z. physiol. Chem.*, **197**, 173 (1931).
[272] Callow, *J. Chem. Soc.*, **1936**, 462.
[273] Wieland and Deulofeu, *Z. physiol. Chem.*, **198**, 127 (1931).
[274] Plattner, Ruzicka, and Holtermann, *Helv. Chim. Acta*, **28**, 1660 (1945).
[275] Bergmann and Skau, *J. Org. Chem.*, **5**, 439 (1940).
[276] Fürst and Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).
[277] Heilbron, Shaw, and Spring, *Rec. trav. chim.*, **57**, 529 (1938).
[278] Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, **27**, 513 (1944).
[279] Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, **16**, 327 (1933).
[280] Reich, Walker, and Collins, *J. Org. Chem.*, **16**, 1752 (1951).
[281] Buser, *Helv. Chim. Acta*, **30**, 1379 (1947).
[282] Plattner, Heusser, Troxler, and Segre, *Helv. Chim. Acta*, **31**, 852 (1948).
[283] Westphalen, *Ber.*, **48**, 1064 (1915).
[284] Fieser and Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).
[285] Clemo, Keller, and Weiss, *J. Chem. Soc.*, **1950**, 3470.
[286] Pirrone, *Atti X° congr. intern. chim.*, **3**, 290 (1939) [*C. A.*, **33**, 9309 (1939)].
[287] Pickard and Yates, *J. Chem. Soc.*, **93**, 1678 (1908).
[288] Hicks, Berg, and Wallis, *J. Biol. Chem.*, **162**, 645 (1946).
[289] Spring and Swain, *J. Chem. Soc.*, **1939**, 1356.
[290] Baxter and Spring, *J. Chem. Soc.*, **1943**, 613.
[291] Ushakov and Lyutenberg, *Bull. soc. chim. France*, [5] **4**, 1394 (1937).
[292] Ushakov and Lyutenberg, *J. Gen. Chem. (U.S.S.R.)*, **7**, 1821 (1937) [*C. A.*, **32**, 577 (1938)].
[293] Miescher and Fischer, *Helv. Chim. Acta*, **21**, 336 (1938).
[294] Ruzicka, Grob, and Raschka, *Helv. Chim. Acta*, **23**, 1518 (1940).
[295] Ruzicka and Muhr, *Helv. Chim. Acta*, **27**, 503 (1944).
[296] Ehrenstein and Decker, *J. Org. Chem.*, **5**, 544 (1940).
[297] Ehrenstein, *J. Org. Chem.*, **6**, 626 (1941).
[298] Ehrenstein, *J. Org. Chem.*, **4**, 506 (1939).
[299] Davis and Petrow, *J. Chem. Soc.*, **1949**, 2973.
[300] Petrow, *J. Chem. Soc.*, **1939**, 998.
[301] Plattner, Ruzicka, Heusser, and Angliker, *Helv. Chim. Acta*, **30**, 395 (1947).
[302] Bergmann and Stevens, *J. Org. Chem.*, **13**, 10 (1948).
[303] Wieland and Dane, *Z. physiol. Chem.*, **206**, 243 (1932).
[304] Windaus and Lüttringhaus, *Ann.*, **481**, 119 (1930).
[305] Ciba, Ltd., Swiss pat. 267,852 [*C. A.*, **45**, 7158 (1951)].
[306] Mattox, Turner, Engle, McKenzie, McGuckin, and Kendall, *J. Biol. Chem.*, **164**, 569 (1946).
[307] Ciba, Ltd., Swiss pat. 253,707 [*C. A.*, **44**, 3042 (1950)].
[308] Dobriner, Lieberman, Hariton, Sarett, and Rhoads, *J. Biol. Chem.*, **169**, 221 (1947).
[309] Lardon and Liebermann, *Helv. Chim. Acta*, **30**, 1373 (1947).
[310] McKenzie, McGuckin, and Kendall, *J. Biol. Chem.*, **162**, 555 (1946).
[311] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).
[312] Wieland, Dietz, and Ottawa, *Z. physiol. Chem.*, **244**, 194 (1936).
[313] Heusser, Feurer, Eichenberger, and Prelog, *Helv. Chim. Acta*, **33**, 2243 (1950).
[314] Julian, Meyer, and Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).
[315] Pataki, Rosenkranz, and Djerassi, *J. Am. Chem. Soc.*, **73**, 5375 (1951).
[316] Ruzicka, Plattner, Heusser, and Pataki, *Helv. Chim. Acta*, **29**, 936 (1946).
[317] Heusser, Jensen, Frick, and Plattner, *Helv. Chim. Acta*, **32**, 1326 (1949).
[318] Reichstein, U. S. pat. 2,503,842 [*C. A.*, **44**, 6892 (1950)].
[319] Press and Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942).
[320] Ruzicka, Plattner, Heusser, and Meier, *Helv. Chim. Acta*, **30**, 1342 (1947).
[321] Heymann and Fieser, *J. Am. Chem. Soc.*, **73**, 4054 (1951).
[322] Berner, Lardon, and Reichstein, *Helv. Chim. Acta*, **30**, 1542 (1947).

[475] Rosenkranz, Pataki, and Djerassi, *J. Am. Chem. Soc.*, **73**, 4055 (1951).

[476] Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, 1891 (1951).

[477] Lieberman, Hariton, Humphries, Rhoads, and Dobriner, *J. Biol. Chem.*, **196**, 793 (1952).

[478] Heusser, Heusler, Eichenberger, Honegger, and Jeger, *Helv. Chim. Acta*, **35**, 295 (1952).

[479] Shoppee and Summers, *J. Chem. Soc.*, **1952**, 1790.

[480] Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Am. Chem. Soc.*, **73**, 2396 (1951).

[481] Constantin and Sarett, *J. Am. Chem. Soc.*, **74**, 3908 (1952).

[482] Ellis and Petrow, *J. Chem. Soc.*, **1952**, 2246.

[483] Kritchevsky, Garmaise, and Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952).

[484] Ames and Bowman, *J. Chem. Soc.*, **1952**, 677.

[485] Raphael, *J. Chem. Soc.*, **1952**, 401.

[486] Lahey and Strasser, *J. Chem. Soc.*, **1951**, 873.

[487] Barton and Brooks, *J. Chem. Soc.*, **1951**, 257.

[488] Manson and Spring, *J. Chem. Soc.*, **1951**, 3332.

[489] Pigulevskii and Starostiva, *Doklady Akad. Nauk S.S.S.R.*, **79**, 261 (1951) [*C. A.*, 46, 3003 (1952)].

[490] Barton and Bruun, *J. Chem. Soc.*, **1952**, 1683.

[491] Bradley, Forrest, and Stephenson, *J. Chem. Soc.*, **1951**, 2877.

[492] Heuberger and Owen, *J. Chem. Soc.*, **1952**, 910.

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